Current Approaches to Multiple Sclerosis Management in Pregnancy

Valeriya A. Malko, Ekaterina A. Sadovnichuk, Gennady N. Bisaga

V.A. Almazov National Medical Research Centre, Saint Petersburg, Russia

Abstract

This article reviews literature data on the impact of multiple sclerosis (MS) on fertility and pregnancy outcomes, the specifics of using diseasemodifying therapies (DMTs), and breastfeeding practices. The results demonstrate that fertility rates in women with MS do not differ from the general population, and the frequency of pregnancy complications, including stillbirths, congenital malformations, and spontaneous abortions, does not exceed population-level rates. A reduction in MS activity is observed during the third trimester of pregnancy; however, the risk of relapses increases by 50% within the first three months postpartum, necessitating timely resumption of therapy. Pregnancy management in women with MS should involve interdisciplinary collaboration between neurologists and obstetricians and gynecologists, personalized therapy adjustments, and patient education about safe treatment strategies. Certain DMTs can be safely used during pregnancy and lactation, though careful benefit-risk assessment remains crucial. Women with MS can successfully plan and carry pregnancies to term without significant untoward effects on outcomes. Developing personalized management strategies for these patients will help minimize risks and improve their quality of life.

Keywords: *multiple sclerosis; pregnancy; fertility; breastfeeding; DMTs*

Source of funding. Supported by the V.A. Almazov National Medical Research Centre.

Conflict of interest. The authors declare no apparent or potential conflicts of interest related to the publication of this article.

For correspondence: 2 Akkuratov St., Saint Petersburg, Russia, 197341. V.A. Almazov National Medical Research Centre. E-mail: malko_va@almazovcentre.ru. Valeriya A. Malko

For citation: Malko V.A., Sadovnichuk E.A., Bisaga G.N. Current approaches to multiple sclerosis management in pregnancy. *Annals of Clinical and Experimental Neurology*. 2025;19(3):73–84.
DOI: https://doi.org/10.17816/ACEN.1378
EDN: https://elibrary.ru/HQMCDW

Received 27.05.2025 / Accepted 28.07.2025 / Published 30.09.2025

Современные подходы к ведению рассеянного склероза во время беременности

В.А. Малько, Е.А. Садовничук, Г.Н. Бисага

Национальный медицинский исследовательский центр имени В.А. Алмазова, Санкт-Петербург, Россия

Аннотация

В статье представлен обзор данных литературы о влиянии рассеянного склероза (РС) на фертильность и течение беременности, об особенностях приёма препаратов, изменяющих течение РС (ПИТРС), и грудного вскармливания. Результаты демонстрируют, что у женщин с РС показатели фертильности не отличаются от общей популяции, а частота осложнений беременности, включая мертворождения, врождённые пороки и спонтанные аборты, не превышает популяционные показатели. Установлено снижение активности РС в III триместре беременности, однако в первые 3 мес после родов риск обострений возрастает на 50%, что требует своевременного возобновления терапии. Ведение беременности у женщин с РС должно включать междисциплинарное сотрудничество невролога и акушера-гинеколога, индивидуальную корректировку терапии и повышение осведомлённости пациенток о безопасных тактиках лечения. Некоторые ПИТРС могут безопасно использоваться в период беременности и лактации, при этом важно учитывать соотношение риска и пользы. Женщины с РС могут успешно планировать и вынашивать беременность без значимого влияния на её исходы. Разработка индивидуальных стратегий ведения таких пациенток позволит минимизировать риски и повысить качество их жизни.

Ключевые слова: *рассеянный склероз; беременность; фертильность; грудное вскармливание; препараты, изменяющие течение рассеянного склероза*

Источник финансирования. Выполнено при поддержке НМИЦ им. В.А. Алмазова Минздрава России.

Конфликт интересов. Авторы заявляют об отсутствии явных и потенциальных конфликтов интересов, связанных публикацией настоящей статьи.

Адрес для корреспонденции: 197341, Россия, Санкт-Петербург, ул. Аккуратова, д. 2. НМИЦ им. В.А. Алмазова. E-mail: malko_va@almazovcentre.ru. Малько В.А.

Для цитирования: Малько В.А., Садовничук Е.А., Бисага Г.Н. Современные подходы к ведению рассеянного склероза во время беременности. *Анналы клинической и экспериментальной неврологии*. 2025;19(3):73–84.
DOI: https://doi.org/10.17816/ACEN.1378
EDN: https://elibrary.ru/HQMCDW

Поступила 27.05.2025 / Принята в печать 28.07.2025 / Опубликована 30.09.2025

Introduction

The global prevalence of multiple sclerosis (MS) is approximately 2.3 million people [1]. In Russia, MS has an incidence rate of 15–55 per 100,000 population. The disease most commonly manifests between the ages of 20 and 50 years. MS is 2.5–3.0 times more common in women than in men, meaning the majority of MS patients are women of reproductive age. Consequently, studying MS effects on fertility, pregnancy, and breastfeeding has become a critical issue [1–4].

Fertility rates among women with MS are lower than in healthy women, likely due not to direct disease effects on the reproductive system, but rather to patients' psychoemotional and physical status, as well as fears surrounding pregnancy and childbirth in the context of chronic illness [5]. Women with MS fear pregnancy both due to risks of disease exacerbations and potential therapy-related fetal effects, highlighting the need for improved patient education about safe pregnancy planning and management strategies [6]. Current approaches to the management of pregnant MS patients requires collaboration between neurologists and gynecologists, with many established concepts having evolved over recent decades. This shift stems from advances in understanding MS pathogenesis, numerous studies on pregnancy outcomes in MS patients, and expanded therapeutic options with disease-modifying therapies (DMTs) [7].

Proper management of women with MS requires understanding the disease's potential impact on preconception counseling, pregnancy, and the postpartum period. Studies confirm no negative effects of multiple sclerosis on fertility, pregnancy, or breastfeeding when proper preparation and pregnancy management are implemented [3, 8]. Compared to the healthy population, MS does not increase the risk of stillbirth, congenital malformations, low Apgar scores, spontaneous abortions, or ectopic pregnancy [9–11]. MS is not a risk factor for complications such as preeclampsia, postpartum hemorrhage, or chorioamnionitis [9, 12]. Additionally, MS does not affect anti-Müllerian hormone levels, follicle-stimulating hormone levels, or ovarian size, although estrogen levels and antral follicle counts are slightly lower, while luteinizing hormone levels are higher compared to the healthy population [6].

Effects of Pregnancy, Delivery, and Breastfeeding on MS

Pregnancy serves as a protective factor against relapses in women with MS: the annualized relapse rate and disease activity gradually decrease by the third trimester, potentially due to elevated hormone levels (17-beta-estradiol, progesterone, prolactin, testosterone) that stimulate anti-inflammatory mediators (interleukin-10) while suppressing pro-inflammatory cytokines (interleukin-6 and -17). This effect may also involve placentaand fetus-derived cytokines that reduce type 1 T-cell immune responses [8, 12–15]. During pregnancy, several myelin repair-promoting factors are produced: the maternal circulating preimplantation factor enhances remyelination, while allopregnanolone (a progesterone metabolite) potentiates gamma-aminobutyric acid (GABA) signaling through oligodendrocyte GABA receptors, thereby stimulating myelin regeneration [14]. Pregnancy does not influence long-term disability accumulation outcomes in MS [6, 14]. However, physiological immunosuppression during gestation may not fully compensate for the withdrawal of DMTs discontinued to mitigate fetal risks, potentially leading to increased MS activity during pregnancy after DMT cessation [13].

MS activity typically increases significantly during the first 3 months postpartum and then gradually decreases over the following year [2, 4, 8, 14, 16]. Risk factors for postpartum relapses include high pre-pregnancy disease activity, relapses during pregnancy, discontinuation of second-line DMTs before or during pregnancy, and delayed resumption of DMTs after delivery [17, 18]. Conversely, early reintroduction of DMTs reduces post-pregnancy relapse risks [13, 16].

Results from retrospective MRI studies during pregnancy and postpartum demonstrated an increased number of T1and T2-weighted lesions during pregnancy without increased gray matter atrophy [14]. Data on gadolinium-enhancing lesions were conflicting: some studies showed no pregnancy-related changes in contrast-enhancing lesions, while others reported increased gadolinium-accumulating lesions postpartum [6, 14]. Studies examining serum neurofilament light chain levels as a biomarker of disease activity and neurodegeneration in MS revealed temporary elevation in untreated postpartum patients. In contrast, patients receiving natalizumab (before and during pregnancy) showed lower neurofilament levels compared to untreated individuals [6].

Data on potential protective role of breastfeeding (BF) in preventing disease exacerbations during the postpartum period were contradictory: while several studies described no effect of BF on MS course, others reported reduced risk and frequency of relapses during BF [4–6, 8, 16–19].

Pregnancy Planning and Management in Patients with MS

Pregnancy planning is a crucial stage of collaboration between the patient, neurologist, and gynecologist, during which healthcare professionals must inform the patient that

pregnancy is not contraindicated in MS provided proper preparation and management are ensured. Therefore, even at the stage of selecting MS therapy, it is essential to clarify with the patient: whether she plans pregnancy (and if so, how long after therapy initiation), her obstetric history, and whether she intends to breastfeed [12] (Table 1).

For women with MS not planning pregnancy, it is important to use effective contraception to prevent unintended pregnancy [6, 14]. Reversible long-acting contraceptive methods (intrauterine device), irreversible permanent methods (tubal ligation), and barrier methods is acceptable, safe, and effective in MS [5, 6]. Long-acting and permanent contraceptive methods may be preferred for patients receiving therapy with proven teratogenic effects [5]. Opinions regarding the use of combined oral contraceptives (COCs) in patients with MS vary [19]. On one hand, earlier studies suggest that COCs may negatively impact the course of multiple sclerosis due to alterations in women's immune status associated with hormonal stimulation; they may also increase the risk of MS by 40% and contribute to a more severe disease course [14, 15]. On the other hand, several authors have demonstrated no association between COCs and the course of multiple sclerosis, even suggesting a possible neuroprotective effect related to changes in hormonal activity during COC use [15, 19]. COCs do not increase the risk of conversion from clinically isolated syndrome to MS [5]. According to the meta-analysis by M. Ghajarzadeh *et al.*, COCs have neither a positive nor negative effect on the course of multiple sclerosis [15]. Progestogen-only contraceptives may have a possible protective effect [14, 15]. Some studies also report that patients taking COCs had lower EDSS scores and reduced annualized relapse rates [2]. To date, there is no definitive understanding of the impact of emergency hormonal contraception on MS course, which underscores the importance of selecting an appropriate long-term contraceptive method [6]. Contraceptive choice should be personalized, considering factors such as drug compatibility, potential contraindications, and reversibility [6]. Interpregnancy contraception reduces the risks of induced abortion, which may trigger MS exacerbations and disease progression due to hormonal stress [6].

When counseling women with MS planning pregnancy, it is crucial to consider their concerns about potential disease exacerbations, MS progression, and challenges of childcare management given their condition [6]. For women planning pregnancy, achieving sustained MS remission prior to conception, adjusting DMTs, and optimizing vitamin/mineral supplementation (e.g., folic acid, vitamin D) are particularly important during pregravid preparation [8, 12]. According to R. Alroughani et al., women who received DMTs for at least two years prior to pregnancy exhibited lower risks of relapses both during gestation and postpartum [20]. Maintaining remission for one year before conception is associated with absence of postpartum MS exacerbations [6]. During pregnancy planning, clinicians should review all medications used for MS symptom management or comorbid conditions (e.g., depression, pain syndrome, anxiety, etc.), as these may impact both hormonal contraceptive efficacy and fetal health [5, 12].

Some medications (particularly cyclophosphamide) used for MS therapy may reduce ovarian reserve and affect

Table 1. Algorithm of managing pregnant women with MS (based on [17])

Before pregnancy	After pregnancy	Postpartum
1. Regular consultations (at least annually) should be conducted to discuss: What type of contraception should be used? Whether the woman is physically capable of pregnancy and how treatment should be adjusted? If pregnancy is not achievable, should assisted reproductive technologies be considered? 2. When preparing for pregnancy, vitamin D and folic acid should be taken in accordance with general recommendations	1. Women with unplanned pregnancies should adjust their DMT regimen and undergo ultrasound examination. Interferon beta and glatiramer acetate may be continued, while other medications should be discontinued as soon as possible: natalizumab may be used until 34 weeks of gestation in cases of high relapse risk. Patients on teriflunomide require an accelerated elimination protocol until plasma drug concentration falls below 0.02 g/L. 2. Maintaining a healthy diet with vitamin D and folic acid supplementation is recommended. 3. Most inactivated vaccines can be administered during pregnancy, whereas live vaccines are generally contraindicated. 4. Relapses may be managed with high-dose methylprednisolone (not dexamethasone) or plasmapheresis. Methylprednisolone can be used starting from the second trimester, and in the first trimester only if maternal benefits outweigh fetal risks of congenital anomalies. 5. Close monitoring is required for urinary tract infections, thromboembolic events, hypothyroxinemia, perinatal depression, and other complications. 6. Multiple sclerosis does not contraindicate any specific delivery method or anesthesia type. The choice should be guided primarily by obstetric indications. 7. MRI necessity should be evaluated case-by-case. A standard 1.5 Tesla protocol is recommended, while gadolinium-based contrast agents should be avoided	1. The woman's wish to breastfeed should be considered. Interferon beta and glatiramer acetate may be continued during BF, while natalizumab and ocrelizumab may be used in select cases. Other DMTs are not recommended. 2. Women at high risk of postpartum relapses should be advised to delay or avoid BF and promptly resume high-efficacy DMTs. 3. The likelihood of relapses increases during the postpartum period. Methylprednisolone and plasma exchange may be used to manage relapses during BF. Breastfeeding may be resumed 4–12 hours after intravenous methylprednisolone administration at the treating physician's discretion. Pharmacological relapse prophylaxis is not recommended. 4. There are no restrictions on MRI use during the postpartum period. Brain MRI is recommended within 2–3 months after delivery, while gadolinium-based contrast agents are not advised during BF

female fertility [14]. Therefore, patients with MS who are not planning pregnancy in the near future may be advised to undergo oocyte cryopreservation or partner sperm preservation before initiating treatment with fertility-affecting agents [8]. The use of fertility-affecting DMTs and the average age of MS onset may necessitate assisted reproductive technologies (ART) [8]. The need for hormonal stimulation of oocyte maturation during ART may lead to increased relapse rates and numbers of active MRI lesions [6, 8, 21]. Studies have shown that the annualized relapse rate may increase following ART using gonadotropin-releasing hormone (GnRH) agonists, which activate autoreactive $CD4^+$ T cells, lead to elevated estrogen levels, and consequently increase proinflammatory factors [5, 14]. However, there is no definitive consensus regarding the association between MS relapse risk and ART. Current evidence suggests that ART protocols using GnRH antagonists may be safer in terms of MS course [6, 19]. When ART is required, it is recommended to achieve stable clinical and radiological remission for at least 12 months before initiating ART and to continue DMTs during ART to reduce relapse risk. When planning pregnancy using ART, patients should be informed about the potential adverse effects of hormonal stimulation [14].

The method of delivery for patients with MS is determined by general obstetric indications; however, obstetricians and gynecologists may unjustifiably opt for cesarean delivery due to excessive caution [13, 14, 22]. Cesarean delivery may be indicated by neurological symptoms that increase the risk of secondary labor dystocia: severe lower paraparesis, weakness of the abdominal muscles, or pelvic organ dysfunction [22–25]. Epidural anesthesia during labor has been shown to have no adverse effects on the course of MS: there is no evidence of increased relapse rates or impact on patient disability [6, 12, 13]. Patients with MS may experience sensory deficits that prevent them from recognizing the onset of labor; therefore, they should be educated about alternative signs indicating the initiation of labor [14].

MRI in Pregnancy

In pregnant patients with MS, routine MRI is not recommended; however, if vital indications are present, the study may be performed at any gestational age. MRI scanners with a magnetic field strength of less than 3 Tesla are permitted [5, 11, 14, 25]. Gadolinium-based contrast agents are not recommended due to their ability to cross the placental barrier, accumulate in the fetal brain, and cause intrauterine fetal demise or developmental abnormalities; their use should therefore be restricted to cases where benefits clearly outweigh risks [5, 12, 14, 25].

Medications Overview and DMT Use Strategy During Pregnancy

Difficulties in prescribing and continuing MS therapy for pregnant women arise from the need to discontinue certain medications due to their teratogenicity [5, 13]. Discontinuation of DMTs increases the risk of MS activity both during pregnancy and postpartum [3, 13, 14]. Currently, the number of patients remaining on DMT therapy during pregnancy decreases by half in the first trimester and sixfold in the second and third trimesters compared to the pre-pregnancy period [26]. Recent studies indicate a significant shift in the perception of DMT safety: continuation of DMT therapy and early resumption of DMTs postpartum are now recommended for all MS patients, as this promotes disease stabilization and reduces the risk of relapses during pregnancy and the postpartum period [4, 5, 7, 16].

According to a retrospective analysis by M. Moccia *et al.* describing data from 2018–2020 in a population of Italian women with MS, continued use of DMTs during pregnancy (glatiramer acetate, interferon beta, and natalizumab) was associated with lower infant birth weight. However, DMT therapy did not affect pregnancy duration, cesarean section rates, congenital malformations, or infant head circumference and length [3]. These data were obtained in comparison with a group that discontinued DMTs after conception. The fetal effects of these agents may be related to their ability to cross the placental barrier: small molecules, predominantly administered orally, penetrate the barrier more easily, unlike large molecules, which are retained due to their size [5].

Interferon Beta and Glatiramer Acetate

For women with MS at high risk of relapses who are planning pregnancy, first-line DMTs such as interferon beta and glatiramer acetate are considered safe due to their large molecular size and limited ability to cross the hematoplacental barrier [14]. Interferon beta and glatiramer acetate were among the first DMTs shown to reduce relapse rates and delay disability progression in MS. According to the study by M. Moccia *et al.*, no cases of congenital malformations were reported in children born to patients who received glatiramer acetate and interferon beta during pregnancy [3]. Interferon beta is not associated with adverse pregnancy outcomes regardless of the timing of administration [7, 27]. However, interferon beta and glatiramer acetate may sometimes be insufficient for disease control, necessitating a switch to second-line DMTs whose safety during pregnancy remains uncertain [28].

Natalizumab

Natalizumab is a monoclonal antibody that can reduce the number and size of active brain lesions while decreasing the frequency of relapses [27]. Although natalizumab can cross the placental barrier, its use during pregnancy is allowed if the potential therapeutic benefits outweigh the risks [12, 14]. Prolonged natalizumab therapy prior to pregnancy significantly improves MS control and reduces the likelihood of relapses during pregnancy and postpartum [28]. Patients who discontinue natalizumab after conception exhibit a higher risk of MS exacerbations and disability progression both during pregnancy and in the postpartum period [4, 5, 12, 29]. Therefore, natalizumab should not be discontinued before pregnancy or during the first trimester, given the elevated risk of severe relapses upon withdrawal (with a ~10% risk of significant disability); instead, therapy should be continued at extended intervals (6–8 weeks) until the third trimester (30–34 weeks gestation), followed by early postpartum resumption to minimize relapse risk [4–6, 12, 30]. Secondand third-trimester natalizumab use is associated with lower

neonatal birth weight and fetal anemia/thrombocytopenia, but does not increase risks of major congenital malformations or spontaneous abortion [3, 5, 12, 28, 30].

Fingolimod

Fingolimod is the first oral agent approved for relapsing MS, effectively reducing relapse rates [27]. Animal studies have demonstrated that fingolimod can cause fetal death and significant congenital anomalies [27]. In a study by M. Moccia *et al.*, 9.1% of women exposed to fingolimod during pregnancy gave birth to children with birth defects [3]. Effective contraception is essential during fingolimod treatment; fingolimod must be discontinued at least 2 months before planned pregnancy, though this carries risks of increased MS exacerbations after discontinuation and severe disability (6%) [4, 5, 12, 27]. The association between fingolimod withdrawal and elevated relapse risk necessitates pregnancy planning with potential transition to alternative fetal-safe therapies capable of controlling MS: first-line DMTs or natalizumab may serve as a therapeutic bridge during fingolimod discontinuation and until conception [31–33]. As fingolimod belongs to agents with a higher risk of withdrawal syndrome, early resumption of therapy during the postpartum period is required.

Siponimod

There is insufficient research on the safety and outcomes of siponimod use during pregnancy [5]. Siponimod is contraindicated during pregnancy and must be discontinued at least 10 days prior to conception [4–6, 8].

Dimethyl fumarate

Data on dimethyl fumarate use during pregnancy are limited, with potential reproductive toxicity in animal studies. Discontinuation is recommended upon pregnancy confirmation, and no washout period is required [6–8, 14, 27]. Use during pregnancy is only permissible if benefits outweigh risks.

Teriflunomide

Teriflunomide has proven teratogenic effects, increasing spontaneous abortion risk by 21–22% [5, 6, 12, 27]. It is contraindicated during pregnancy and requires a washout period until plasma concentrations fall below 0.02 mg/L before conception [4, 7, 12, 27]. Patients must be advised to use contraception during the washout period to prevent unintended pregnancy [12]. Teriflunomide is detectable in semen, necessitating contraceptive measures for males during treatment and washout. Additionally, men should be informed about potential fertility reduction during therapy [34].

Alemtuzumab

The fetal risks associated with alemtuzumab continue to be studied, but it cannot be ruled out that alemtuzumab use later than 4 months before pregnancy may increase the risk of spontaneous abortion and neonatal thyrotoxicosis due to transplacental transfer of thyroid autoantibodies [5, 12, 25, 27, 35]. Studies indicate that the most common pregnancy outcome following alemtuzumab exposure is an uncomplicated pregnancy; however, there is no conclusive evidence regarding the drug's safety [3, 7, 14, 36]. In women with MS receiving alemtuzumab, no increased risk of hypertension, eclampsia, preeclampsia, or postpartum hemorrhage was observed compared to healthy women, though elevated risks of autoimmune thyroid disorders and infectious diseases were noted [14, 27, 35]. Thyroid function should be monitored during treatment and when planning pregnancy. According to prescribing guidelines, the agent must be discontinued at least 4 months prior to conception [3, 4, 6, 14, 27].

Cladribine

The safety of cladribine during pregnancy remains debated: some studies show most infants exposed to cladribine during gestation are born without severe congenital malformations, though animal studies suggest potential reproductive toxicity [3, 5, 6, 14, 37]. Cladribine should be discontinued 6–12 months before planned pregnancy [3–5, 8, 25].

Mitoxantrone

Mitoxantrone is teratogenic and contraindicated for use during pregnancy. Prior to initiating therapy, healthcare providers must confirm the patient is not pregnant, has no pregnancy plans, and is using effective contraception. Discontinuation of mitoxantrone is recommended at least 4–6 months prior to pregnancy [7, 25, 27, 38].

Anti-CD20 Monoclonal Antibodies

The safety of ocrelizumab during pregnancy is under discussion. Use of the agent during pregnancy may lead to toxic effects on the reproductive system [14, 27, 35]. Ocrelizumab should be discontinued 6–12 months before conception [4–6, 12, 35, 39].

Rituximab during pregnancy poses potential risks to the fetus, including preterm birth and congenital malformations [27, 35]. Rituximab must be discontinued 6–12 months prior to pregnancy [35].

Rituximab and ocrelizumab during pregnancy may cause fetal B-cell depletion with gradual recovery over 6 months [5, 12]. This should be considered when administering live vaccines to newborns: vaccination timing should be individualized based on B-cell levels [5].

Limited studies of ofatumumab have not demonstrated fetal toxicity; however, it can cross the transplacental barrier and reduce fetal B-cell counts [5, 35]. Ofatumumab is contraindicated during pregnancy; due to limited safety data, it should be discontinued 6 months before pregnancy [5, 8, 12, 27, 35].

$CD20^+$ B-cell-targeting agents (ocrelizumab, rituximab, and ofatumumab) may serve as preferred options for managing patients in the postpartum period due to their efficacy and safety profile during high relapse-risk phases [6]. They may

also be used as bridging therapy shortly before or immediately after delivery for patients declining natalizumab or fingolimod based on individual indications, to reduce relapse risks [5, 12, 37].

Exacerbation Treatment

Exacerbations of MS during pregnancy should be treated with short courses of methylprednisolone, as unlike dexamethasone, it is metabolized in the maternal body before crossing the placental barrier [14, 28]. Dexamethasone may be associated with lower birth weight and length [5, 14]. In cases of inadequate response to glucocorticosteroids, plasmapheresis is recommended [5, 14, 3].

Therapy During Breastfeeding

An important factor in selecting MS therapy during the postpartum period is the woman's wish to breastfeed. All DMTs, except for interferon beta, are not considered absolutely safe for the child during breastfeeding [4, 8, 12, 14]. This factor raises the question of discontinuing breastfeeding if early resumption of other MS therapies is required. Although interferon beta can penetrate breast milk in small concentrations, no proven association with adverse effects on the child's growth and development has been established [27].

Glatiramer acetate may be used during breastfeeding, but its necessity should be evaluated based on maternal benefit and the agent's ability to pass into breast milk in small concentrations, despite the lack of data on negative effects on the child [4, 8, 12, 27].

Natalizumab is detected in breast milk in small concentrations, with no observed long-term health consequences for the child [12, 27]. However, the European Medicines Agency recommends avoiding natalizumab during breastfeeding [8, 12]. The decision to use natalizumab during BF should be made based on individual indications with a benefit-risk assessment [8, 14].

Breastfeeding can be resumed one week after the last dose of cladribine [8].

Alemtuzumab therapy requires discontinuation of BF during the treatment course and for 4 months after the last administration [8, 14].

Recent evidence suggests that $CD20^+$ cell-targeting drugs may be safe during BF with regular pediatric monitoring [8]. While rituximab demonstrates potential toxicity during BF, no adverse effects have been reported with ocrelizumab [27]. After ocrelizumab administration during ongoing BF, a 4-hour pause before the next feeding is recommended [8].

Mitoxantrone, fingolimod, siponimod, dimethyl fumarate, and teriflunomide are contraindicated during BF due to potential infant toxicity [8, 14, 27].

Prophylactic glucocorticosteroid treatment for postpartum relapses is not recommended [14]. Methylprednisolone is the option of choice for acute relapse management, with minimal breast milk concentration [12, 14]. The prescribing information advises against methylprednisolone use during BF due to milk penetration, though plasma concentrations decrease to undetectable levels within 18 hours (extremely low levels within 12 hours). Research indicates methylprednisolone concentrations in breast milk reach safe levels within 2–4 hours post-administration, allowing clinical discretion in its use [5, 12, 25]. Plasmapheresis may be considered for breastfeeding women with severe methylprednisolone-resistant relapses [25]. Summary of DMT use in MS patients is presented in Table 2.

Conclusion

Management of pregnancy in multiple sclerosis requires a multidisciplinary team approach. It is crucial to evaluate the impact of current therapy on pregnancy and breastfeeding, the need for treatment modification, risks to the mother and fetus, and select appropriate contraception if pregnancy postponement is necessary. Safe contraception should also be selected for patients wishing to avoid pregnancy. Unintended pregnancy and abortion may trigger MS exacerbations. COCs may be used in MS patients, but their safety remains controversial.

MS does not reduce fertility and is not a contraindication to pregnancy or childbirth, but requires careful planning and monitoring. ART may increase relapse risk, necessitating achievement of stable remission prior to ART and use of GnRH antagonist protocols from the perspective of MS exacerbation risk management.

DMT selection depends on both MS type and patient's reproductive plans. While not all therapies are fetal-safe, treatment discontinuation carries risks of relapses and disability progression. The only agents with proven safety during pregnancy are interferon beta and glatiramer acetate. Other agents require individual risk-benefit assessment. When discontinuing therapy, washout periods and required contraceptive coverage must be considered.

Postpartum MS exacerbation risk increases, necessitating prompt DMT resumption with consideration of BF status. Interferon beta and glatiramer acetate are considered safe during BF, while other agents require dose adjustment or BF discontinuation. Postpartum treatment selection should account for maternal breastfeeding preferences and adjust therapy accordingly.

Table 2. Use of disease-modifying therapies for multiple sclerosis before pregnancy, during pregnancy, and during lactation

Drug Product	Contraception before pregnancy	Use during pregnancy	Use during lactation
		Interferon beta	
Interferon beta-1a (Rebif, Teberif) (GRLS)	Not required	Use may be considered following risk assessment by the treating physician Duration of use in the first trimester is undetermined; experience with use in the second and third trimesters is very limited No increased risk of congenital malformations prior to conception and/or during the first trimester of pregnancy	May be used. The amount of drug excreted into breast milk is negligible; no adverse effects on infants are anticipated
Interferon beta-1a (Plegridy) (GRLS)	No information in the label	Available data are insufficient to adequately assess the risk of spontaneous abortion in pregnant women using drugs of the same class; however, they do not indicate an increased risk. Use of the drug may be considered by the treating physician based on clinical necessity	Available data suggest that the amount of drug excreted into breast milk is negligible. No adverse effects on the newborn/breastfed infant are anticipated. Use during breastfeeding is allowed
Interferon beta-1a (Genfaxon, CinnoVex) (GRLS)	Women of reproductive potential should use effective contraceptive methods	Contraindicated	Data on drug excretion into breast milk are unavailable; a choice must be made between discontinuing the drug or ceasing breastfeeding
Interferon beta-1b (Infibeta) (GRLS)	No information in the label	No harmful effects on the newborn/child are anticipated with drug use during pregnancy. In cases of clinical necessity, the treating physician should decide on the possibility of using interferon beta-1b during pregnancy if the expected benefit of the drug outweighs the potential risk of its use	Can be used during breastfeeding. No harmful effects on the breastfed infant are anticipated
Sampeginterferon beta-1a (Tenexia) (GRLS).	No information in the label	Contraindicated	Contraindicated
		Glatiramer acetate	
Axoglatiran FS (GRLS)	No information in the label	Contraindicated	It is unknown whether glatiramer acetate or its metabolites pass into breast milk. The expected therapeutic benefit for the mother should be weighed against potential risks to the child
Timexon, Copaxone Teva, Copaxone 40, Glatirat, Glatsetat (GRLS)	Not required	Not recommended except when maternal benefit outweighs potential fetal risk	May be used. No adverse effects on newborns are anticipated

For continuation of the Table 2, see page 80.

Drug Product	Contraception before pregnancy	Use during pregnancy	Use during lactation
		Teriflunomide	
Femorix, Teriflunomide, Teriflunomide Kanon, Teriflunomide PSK, Teriflunomide-Chemrar, Dissemil (GRLS)	Discontinue 24 months prior to conception Measure drug concentration prior to pregnancy planning; if two measurements 14 days apart show < 0.02 mg/L, no waiting or accelerated elimination is needed. Embryofetal toxicity risk in males is considered low	Contraindicated	Contraindicated
		Dimethyl fumarate	
Eumileo, Fluterio, Dimethyl fumarate (GRLS)	Throughout the entire treatment course	Limited data available. Demonstrated toxic effects on reproductive system. Should only be prescribed in critical cases where maternal benefit outweighs potential fetal risk	Decision should be made after thorough benefit-risk assessment for mother and child
		Fingolimod	
Nescler, Gilenya, Sclimod, Modena, Fingolimod Native, Lifespan, Fingolimod, Fingolimod Medisorb (GRLS)	Throughout treatment and 2 months after discontinuation	Drug discontinuation should be considered, weighing maternal benefits against fetal risks, due to severe relapses after withdrawal. Reproductive toxicity	Contraindicated
		Natalizumab	
Tysabri (GRLS)	No instructions	Should only be used in critical cases. Newborns should be monitored for platelet count and hemoglobin levels	Breastfeeding must be discontinued during drug therapy. Excreted in breast milk
Expert consensus opinion [5, 25]	Not required	Discontinue at 30–34 weeks gestation with extended dosing interval (6–8 weeks), then resume 1–2 weeks postpartum. Alternative approach: Switch to another DMT before pregnancy to reduce relapse risk, particularly in patients with PML risk and JC virus antibodies. Newborn blood parameters (LDH, bilirubin, hemoglobin) require monitoring when used in 2nd/3rd trimester	May be used. No interval required between infusion and subsequent breastfeeding
		Alemtuzumab	
Lemtrada (GRLS)	Throughout treatment and 4 months post-treatment	May be used if maternal benefit outweighs fetal risk. Placental transfer of TSH receptor antibodies causing neonatal Graves' disease has been reported. Untreated hypothyroidism in pregnancy increases miscarriage risk and fetal complications including mental retardation and dwarfism	Breastfeeding benefits should be balanced against maternal clinical need and potential adverse effects of alemtuzumab/maternal disease on infant. Breastfeeding prohibited during treatment and 4 months post-infusion

For continuation of the Table 2, see page 81.

Drug Product	Contraception before pregnancy	Use during pregnancy	Use during lactation
		Ocrelizumab	
Ocrevus (GRLS)	Throughout treatment and 12 months post-treatment	Should be avoided unless benefit outweighs risk Limited data available. Possible B-cell depletion and lymphocytopenia in newborns. Animal studies showed no teratogenic effects but demonstrated reproductive toxicity	Breastfeeding should be discontinued during therapy. Risk cannot be ruled out
Expert consensus opinion [5, 25]	Conservative approach: pregnancy is possible 3 months after the last infusion. Active approach: pregnancy in the next menstrual cycle	In the absence of absolute indications, discontinuation of ocrelizumab during pregnancy is recommended. Decrease in B-cell counts in newborns and a slight increase in the risk of preterm birth and low birth weight were observed in a study involving < 30 pregnancies in women	May be used; a waiting period of ≥ 4 hours after antihistamine administration is required before the next breastfeeding session
		Divozilimab	
Ivlizi (GLRS)	Throughout treatment and 12 months post-treatment	Contraindicated. Should not be used during pregnancy, except in cases where the benefit to the mother outweighs the potential risk to the fetus. Some newborns of mothers treated with anti-CD20 antibodies during pregnancy showed transient depletion of peripheral B-cell pools and lymphocytopenia	Not recommended during treatment with the drug. No data available on potential drug excretion into breast milk
		Ofatumumab	
Bonspri (GLRS)	Throughout treatment and 6 months post-treatment	Contraindicated due to lack of safety data for this therapy. Animal studies showed no reproductive toxicity	Contraindicated due to insufficient safety data
Expert consensus opinion [5, 25]	Either a conservative approach (discontinuing the drug when attempting pregnancy) or an active approach (administering the drug until conception occurs, with injections timed to menstrual periods) is recommended	Limited data (30 pregnancies) show no congenital anomalies. Seventeen live births have been reported	The drug can be safely used 2 weeks postpartum, with no required interval between breastfeeding and infusion
		Cladribine	
Mavenclad (GRLS).	Both men and women must use contraception for 6 months after the last dose	Women who become pregnant during therapy should discontinue the drug. Animal studies demonstrated reproductive toxicity	No data available on drug excretion into breast milk. Breastfeeding should be discontinued during therapy and for 1 week after the last dose
		Siponimod	
Kajendra (GRLS)	Throughout treatment and 10 days post-treatment	Contraindicated. Animal studies demonstrated embryoand fetotoxicity	Contraindicated. Unknown whether it penetrates breast milk

Note. GRLS — the drug prescribing information in Russia is derived from the State Register of Medicinal Products (Russian abbreviation: *GRLS*). Green — safe for use during pregnancy; yellow — use during pregnancy is permissible if maternal benefit outweighs fetal risk; red — contraindicated for use during pregnancy.

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Information about the authors

Valeriya A. Malko – assistant, Department of neurology with the clinic, Medical Education Institute, Almazov National Medical Research Centre, St. Petersburg, Russia, https://orcid.org/0000-0003-2230-3750
Ekaterina A. Sadovnichuk – student, Faculty of medicine, Medical Education Institute, Almazov National Medical Research Centre, St. Petersburg, Russia, https://orcid.org/0009-0007-6275-2725
Gennady N. Bisaga – Dr. Sci. (Med.), Professor, Department of neurology with the clinic, Medical Education Institute, Almazov National Medical Research Centre, St. Petersburg, Russia, https://orcid.org/0000-0002-1848-8775

Author contribution. *Malko V.A.* – formulation and elaboration of the goal, collection and processing of material, writing of the text; *Sadovnichuk E.A.* – collection and processing of material, writing of the text; *Bisaga G.N.* – management and coordination of work, editing of the text.

Информация об авторах

Малько Валерия Алексеевна – ассистент кафедры неврологии с клиникой НМИЦ им. В.А. Алмазова, Санкт-Петербург, Россия,
https://orcid.org/0000-0003-2230-3750
Садовничук Екатерина Александровна – студентка 5-го курса НМИЦ им. В.А. Алмазова, Санкт-Петербург, Россия,
https://orcid.org/0009-0007-6275-2725
Бисага Геннадий Николаевич – д-р мед. наук, профессор кафедры неврологии с клиникой ИМО НМИЦ им. В.А. Алмазова, Санкт-Петербург, Россия, https://orcid.org/0000-0002-1848-8775

Вклад авторов. *Малько В.А.* – формулирование и проработка цели, сбор и обработка материала, написание текста; *Садовничук Е.А.* – сбор и обработка материала, написание текста; *Бисага Г.Н.* – руководство и координация работ, редактирование текста.