Multiple Sclerosis and Women's Reproductive Health: From Conception to Postpartum

ARTICLE INFO

Article Type

Review Article

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Received: 02 May, 2023
Accepted: 14 June, 2023
e Published: 07 November 2023

Article History

ABSTRACT

Multiple sclerosis (MS) is a chronic neurological disorder affecting over 2.8 million individuals globally. The relapse rate of MS is typically reduced during late pregnancy but increases in the postpartum period. Historically, women with MS have been advised against pregnancy due to concerns about reproduction. Studies have examined the influence of childbirth methods on the risk of MS. Pregnant MS patients have several delivery and anesthesia options available to them. Vaginal delivery can be considered as a safe option unless there are specific obstetric indications for cesarean section. Neuraxial anesthesia, such as epidural anesthesia, can be used for pain management during delivery. Close monitoring of disease activity during pregnancy and the postpartum period is essential, and the use of DMTs should be carefully evaluated on an individual basis. Collaboration between the patient's neurologist and obstetrician is crucial to ensure optimal outcomes for both the mother and the baby. Also, further research is needed to understand the issues related to treatment during breastfeeding.

Keywords: Multiple sclerosis (MS); Reproductive Health; Conception; Postpartum; Disease modifying therapy (DMT).

[DOI: 10.61186/sjrm.8.1.67]

Introduction

Multiple sclerosis (MS) is a chronic neurological disorder characterized by a female predominance, affecting over 2.8 million individuals globally, with a female-to-male ratio of approximately 3:1 (1). Women diagnosed with MS often encounter multifaceted challenges associated with reproduction, pregnancy, and menopause, all while managing the complexities of their underlying disease. A large prospective study, aimed to assess the influence of pregnancy and delivery on the clinical course of MS. It found that the relapse rate of MS is typically reduced during late pregnancy but increases in the postpartum period. Pregnancy entails a series of significant physiological alterations, including hypercoagulability, insulin resistance, immunotolerance towards the fetoplacental unit, and augmented plasma volume. Adaptation to these physiological changes can be particularly challenging in the context of chronic illness (2). Although the precise etiology of MS remains elusive, genetic factors and environmental elements such as vitamin D levels, smoking, air pollution, and Epstein-Barr virus infection have been proposed as potential predisposing factors (3).

Assessing Disease Activity in Multiple Sclerosis

The assessment of disease activity in MS involves clinical evaluation based on the frequency and severity of relapses and magnetic resonance imaging (MRI) to detect new or enlarged lesions in the brain and spinal cord. Disability progression is evaluated using the Expanded Disability Status Scale (EDSS) (4). Historically, women with MS have been advised against pregnancy due to concerns about their ability to care for their children, given t¬he potential for fatigue and disability. Additionally, worries about transmitting genetic susceptibility to autoimmune conditions to their offspring have also been a consideration. While there is no conclusive evidence suggesting impaired fertility in women with MS, recent research suggests a potential decrease in ovarian reserve among MS patients. Notably, infertility rates in women with MS may be similar to those in the general population, ranging from 10% to 20% in Western countries (5).

Childbirth Methods and Risk of MS Development

The influence of childbirth methods, particularly the use of caesarean section (CS), has been the subject of scrutiny regarding its potential implications for the subsequent risk of offspring developing multiple sclerosis (MS). Researchers have explored this relationship, hypothesizing that CS might affect the risk of MS through modifications in gut microbiota composition, given the growing recognition of the gut-brain axis in neurologic disorders. However, it is important to note that the body of existing research on this topic has produced inconclusive and inconsistent results. Various studies have ventured into investigating the potential link between CS delivery and the risk of MS in later life. Some studies have suggested a potential association, while others have failed to establish a clear connection. The intricacies of the gut microbiome and its role in immune system modulation have made this line of research particularly intriguing. However, the mechanisms through which CS might influence gut microbiota composition and subsequently impact the risk of MS remain a subject of ongoing investigation. Understanding the relationship between CS and MS risk in offspring is a complex endeavor. Factors such as genetic predisposition, environmental influences, and the interplay between the microbiome and the immune system add layers of complexity to this research. Consequently, further investigations are needed to elucidate the potential mechanisms and clarify the relationship between childbirth methods and the risk of MS development in the offspring. (5,6). Approximately 85% of individuals with MS initially present with relapsing-remitting disease (RRMS), characterized by recurrent neurological deficits (relapses) followed by either complete or partial recovery. Given that MS typically manifests before the age of 40, pregnancy becomes a crucial consideration for women with MS. While evidence from the past two decades indicates a substantial reduction in inflammatory disease activity during pregnancy, the effect on the risk of postpartum disease rebound remains less clear (7).

Managing MS in Pregnancy

Neurologists managing women with MS seeking to become pregnant must adopt a benefit-risk approach and offer comprehensive guidance to their patients. Physicians should also be prepared for situations in which women inadvertently continue taking disease-modifying drugs (DMDs) during pregnancy, as many pregnancies occur without prior planning. Balancing the risks of DMDs during pregnancy against the risk of inadequate treatment for the mother is essential, as discontinuing an effective drug may trigger a relapse (7).

Various disease-modifying therapies have emerged for MS management, but most are not recommended for use during pregnancy. Consequently, women with MS face the challenge of striking a balance between managing their disease and ensuring the health of their developing fetus. While research pertaining to women's health issues in the context of MS has grown over time, knowledge gaps persist (9).

[DOI: 10.61186/sjrm.8.1.67]

Fundamental counseling practices emphasize the importance of addressing vitamin D deficiency, which is associated with an increased risk of MS. Women with MS should have their vitamin D levels evaluated and managed before pregnancy. Additionally, women planning to become pregnant should receive guidance on taking prenatal vitamins, folic acid supplementation, avoiding alcohol and smoking, and adopting good sleep hygiene and dietary habits (10).
Pregnancy induces an immunotolerant state, leading to the suppression of clinical and MRI-based disease activity, particularly during the third trimester. This observation has spurred investigations into sex hormone therapy as a potential MS treatment (8). (Table 1)

Disease-Modifying Therapy (DMT)	Dosage and Product Names	Pregnancy Classification (USA/Europe)*	Recommended Pre-Pregnancy Washout	Safe During Pregnancy	Compatibility with Breastfeeding
Interferon beta (IFNβ)	Subcutaneous IFNβ-1b 250 µg every other day (Betaseron, Extavia)	Categorized as C/Category 2	Likely unnecessary during pre-pregnancy period	Likely acceptable during pregnancy (0–1 month)	Likely acceptable (at levels 0.006% of maternal dose)
	Intramuscular IFNβ-1a 30 µg weekly (Avonex)		---	---	---
	Subcutaneous PEG IFNβ-1a 125 µg every 2 weeks (Plegridy)		---	Likely acceptable during pregnancy	---
	Subcutaneous IFNβ-1a 44 or 22 µg 3 times weekly (Rebif)		---	---	---
Glatiramer acetate	Subcutaneous 40 mg 3 times weekly or 20 mg daily (Copaxone, Glatopa)	Categorized as B/Category 2	Not deemed necessary	Likely acceptable during pregnancy	Likely acceptable during breastfeeding
Fingolimod	Oral 0.5 mg daily (Gilenya)	Categorized as C/Category 2	A washout period of 2 months prior to conception	Not recommended during pregnancy	Best avoided (no data available)
Teriflunomide	Oral 14 mg (7 mg in the USA) daily (Aubagio)	Categorized as X/Category 1 (pregnancy must be ruled out prior to use)	An accelerated elimination procedure until blood levels fall below 0.02 µg/ml	Not recommended during pregnancy	Best avoided (no data available)
Dimethyl fumarate	Oral 240 mg twice a day (Tecfidera)	Categorized as C/Category 2	Likely unnecessary during the 0–1 month pre-pregnancy period	Not recommended during pregnancy	Best avoided (no data available)
Natalizumab	Intravenous 300 mg monthly (Tysabri)	Categorized as C/Category 2	Likely unnecessary during the 0–1 month pre-pregnancy period	Can be considered for very active patients	Present in breast milk
Alemtuzumab	Intravenous 12 mg daily for 5 days in the first year, 3 days in the second year (Lemtrada)	Categorized as C/Category 1	A washout period of 4 months prior to conception	Not recommended during pregnancy	Best avoided (no data available)
Mitoxantrone	- Intravenous 12 mg/m² every 3 months (lifetime max 140 mg/m²) (Novantrone)	Categorized as D/Category 2 (pregnancy must be ruled out prior to use)	A washout period of 6 months prior to conception	Not recommended during pregnancy	Best avoided (still present in breast milk at 4 weeks)

Regarding Delivery and Anesthesia Options in Pregnant MS Patients

Regarding delivery and anesthesia options, MS itself does not elevate the risk of high-risk pregnancies, and the duration of hospitalization during childbirth remains unaffected. Anesthetic and delivery method choices are primarily obstetric decisions, with the exception of pregnant women with more pronounced disability, for whom cesarean section may be considered. The first three months postpartum represent a high-risk period characterized by increased clinical and MRI-based disease activity, potentially linked to the rapid reversal of late pregnancy hormone levels. Counseling should address the increased postpartum relapse rate and potential modifiers, including preconceptional DMD use and exclusive breastfeeding (14). The frequency of MS attacks during pregnancy and before pregnancy serves as a significant predictor of postpartum recurrence risk. This association may be attributed to fluctuations in cellular and humoral immunity during pregnancy and post-delivery (15). The use of neuraxial anesthesia/analgesia, such as epidural anesthesia, during delivery in MS patients has been a topic of concern. However, a study including a large number of deliveries did not find any evidence of neuraxial anesthesia/analgesia being associated with disease course in MS. Therefore, neuraxial anesthesia can be considered as a safe option for pain management during delivery in MS patients (16).

Breastfeeding and MS

Breastfeeding offers numerous physical and psychological advantages for both infants and mothers. Increasing evidence suggests that foregoing breastfeeding is generally unnecessary for the majority of women with MS, and exclusive breastfeeding can be encouraged, especially for those with milder disease, on a case-by-case basis (17). Decisions regarding breastfeeding should be tailored to

[DOI: 10.61186/sjrm.8.1.67]

individual circumstances, with patients receiving thorough information and their preferences being considered. Further research, including post-marketing clinical registries and prospective clinical trials, is warranted to enhance understanding of treatment-related issues during breastfeeding (17).

Conclusion

In conclusion, pregnant MS patients have several delivery and anesthesia options available to them. Vaginal delivery can be considered as a safe option, unless there are specific obstetric indications for cesarean section. Neuraxial anesthesia, such as epidural anesthesia, can be used for pain management during delivery. Close monitoring of disease activity during pregnancy and the postpartum period is essential, and the use of DMTs should be carefully evaluated on an individual basis. Collaboration between the patient's neurologist and obstetrician is crucial to ensure optimal outcomes for both the mother and the baby.

Ethical Issue

There was no ethical issue in this review.

Conflict of Interests

There was no conflict of interest in this study.

Source of Funding

This study has been financially supported by Sarem Gynecology, Obstetrics and Infertility Research Center, Sarem Women's Hospital

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[DOI: 10.61186/sjrm.8.1.67]