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Case Report

Is Pregnancy Protective from Rebound After Fingolimod Cessation?

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Multiple sclerosis (MS) is a demyelinating neuroimmunological disease that poses significant reproductive challenges for affected women during pregnancy, particularly in relation to disease-modifying therapies (DMTs). Clinical evidence suggests that while pregnancy may exert a protective effect against relapses, severe rebound disease activity can occur following the discontinuation of certain medications such as fingolimod. This case report describes a pregnant woman, age 46 years, with known MS who experienced a rebound phenomenon after abruptly stopping her DMT. She was managed acutely with intravenous methylprednisolone and rituximab. Following high-potency treatment, the patient demonstrated clinical improvement and maintained a stable postpartum course. This case highlights the complexities of managing MS during pregnancy and underscores the need for individualized therapeutic strategies, structured preconception counseling, and careful planning of DMT discontinuation to prevent severe rebound and optimize both maternal and fetal outcomes.

Keywords: Cessations; Pregnancy; Disease Modifying Therapy; Fingolimod; Multiple Sclerosis; Rebound; Relapse; Sphingosine 1-Phosphate Receptor

Multiple sclerosis (MS) is a demyelinating neurological disorder that affects the central nervous system (CNS) through an inflammatory and autoimmune process. These processes mainly target the white matter of the CNS, which may present in different pictures, including sensory, motor, cognitive and autonomic features, with acute symptoms that can extend to chronic disabilities. It is believed pregnancy is a protected period in MS patients due to the hormonal changes during that time,[1] though relapses and rebound syndrome can still occur.

Progress in understanding MS has led to evolution of many disease-modifying therapies (DMTs). Nevertheless, these therapies require prolonged timelines for approval to ensure their efficacy in treating MS and their safety during childbearing age and pregnancy, as the disease may produce multiple reproductive challenges for this specific population. It could even influence family planning of conception in the first place.[2]

Rebound is defined as a severe new disease activity after discontinuing a DMT, which might be worse than the pre-treatment condition.[3] It usually occurs within 4-16 weeks after DMT cessation, with natalizumab and fingolimod being the most associated medications. Fingolimod is the first oral DMT and the medication of interest in this report. It acts as a sphingosine-1-phosphate (S1P) receptor modulator, known to have an increased rebound risk after an abrupt treatment cessation, necessitating a switch to another DMT. Fingolimod is also associated with high teratogenicity risk (Category C), requiring an 8-week washout period before pregnancy.[2,3]

In this report, we discuss a case of a female patient diagnosed with relapsing remitting multiple sclerosis (RRMS) who

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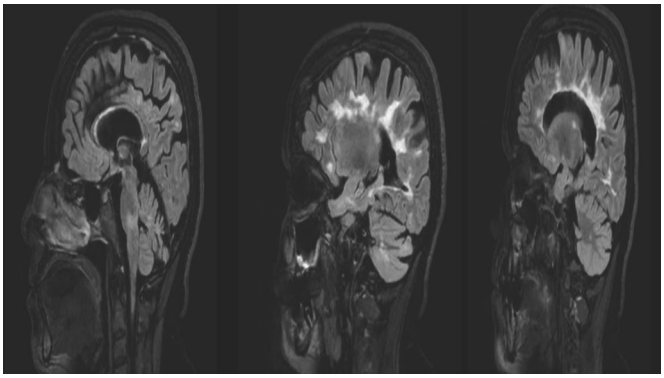

Figure 1. MRI head, Sagittal view, FLAIR. during the acute phase of rebound.

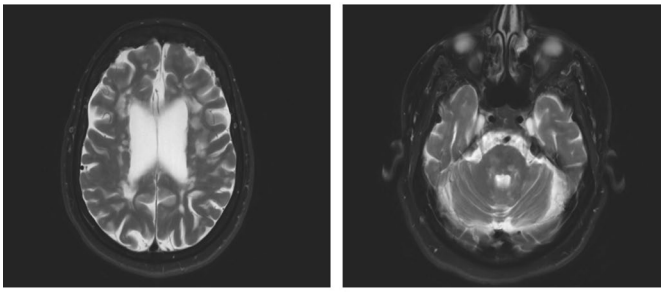

Figure 2. MRI head, Axial view, T2. during the acute phase of rebound.

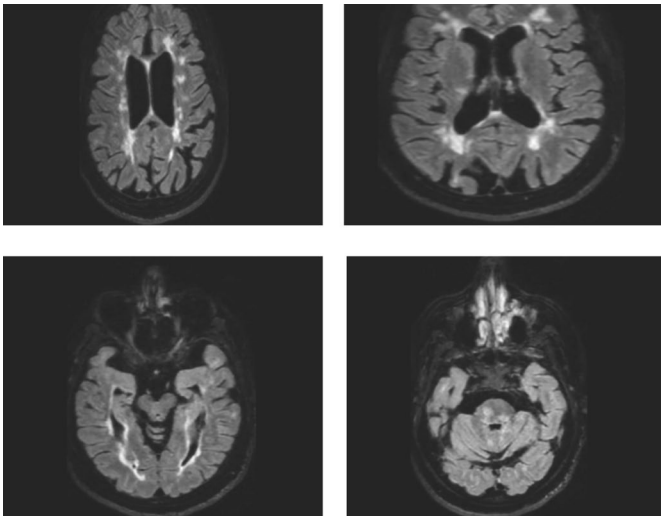

Figure 3. MRI Head, Axial view, Flair. during the acute phase of rebound.

experienced severe rebound and disease reactivation after abruptly discontinuing medication during pregnancy. It provides an overview of similar conditions in the literature, discussing management approaches, follow-up condition as part of this study.

Case Report

The case involves a woman, age 46 years, the mother of five healthy children, with non-contributory family, obstetrical, and gynecological history. She was diagnosed with RRMS at the age of 21 years in 2003. She was initially started on interferon Beta 1a (Rebif) and maintained on it for 18 years until 2020 with good compliance and optimal doses. Her follow-up during this period showed stable disease with no evidence of activity with a baseline Expanded Disability Status Scale (EDSS) of 2.

In 2020, she experienced a new disabling relapse with symptoms affecting her motor function and gait. She was also experiencing injection site burden with the interferon. Because of these two factors, it was decided to escalate treatment to fingolimod at the age of 41. She continued on fingolimod for 3 years without proper contraceptive methods; however, at the age of 44, she had an unplanned pregnancy and discontinued fingolimod abruptly at the 7th week of gestation. She was concerned about teratogenicity but was not aware of the rebound risk and did not consult her primary neurologist.

For 5 months of her pregnancy, she remained symptom-free, until she experienced another attack with severe ataxia affecting her gait and balance, along with left upper limb weakness and numbness, leading to mobility issues and reliance on a wheelchair. At 33 weeks of pregnancy, she sought medical advice and received a 5-day course of intravenous methylprednisolone and was admitted to the hospital. Further investigations, including brain magnetic resonance imaging (MRI), revealed extensive white matter lesions involving the periventricular area and infratentorial regions (MRI; Figure 1-3), with progression compared to her most recent baseline images, which were taken approximately 6 months before pregnancy. Her EDSS was 6. She was initiated on rituximab infusion at an optimal dose of 375 mg/m2, with plans for two doses and regular doses thereafter every 6 months as per routine medication protocol. While her symptoms slightly responded to steroid therapy, she did not receive the second dose of rituximab, as she did not wish to be exposed to multiple medications during pregnancy and preferred not to complete the course of medication. However, she did not return to her baseline before pregnancy.

Throughout the pregnancy, investigations of her unborn fetus showed normal intrauterine growth parameters, including weight and biophysical markers. At the end of the third trimester, she underwent an elective Cesarean section and delivered a healthy baby girl weighing 3.4 kg, without

complications or fetal anomalies. During the postpartum period, approximately 4 months after delivery, she was restarted on rituximab infusion. At that point, 6 months had passed since her first rituximab infusion. She was maintained on regular doses of rituximab and followed up for one year in the neurology clinic.

Three months after delivery investigations, including head and spine MRIs, showed stable disease activity (Figures 4–6.) Follow-up spinal MRI showed no progression, and she showed significant improvement in her clinical condition in terms of mobilization. Her current EDSS score upon follow-up in January 2024 was 3.5.

Discussion

During pregnancy, MS relapses are often decreased; however, attacks can still occur in certain situations, influenced by disease severity, relapse rates, and prior DMT use.[4] For patients who are already on DMT before pregnancy, decisions about stopping, switching, or continuing treatment depend on the DMT class and disease activity. Some DMTs are safe to resume during pregnancy, while others, fingolimod for example, require a washout period to decrease the risk of fetal teratogenicity.[4] Females on such DMTs are instructed to be on a contraceptive method and consult their primary physicians when planning for pregnancy. Structured preconception counselling is strongly recommended to help patients plan DMT transitions safely and minimize risks for both mother and child.

The cessation of certain DMTs, like natalizumab and fingolimod, significantly increases the rebound risk, which requires specific consideration before discontinuation.[3] Patients may self-discontinue fingolimod due to unplanned pregnancies, as seen in our case, where the patient stopped fingolimod and developed severe neurological manifestations in her second trimester.

Our patient had a presentation that suggested a rebound secondary to fingolimod cessation. Some published articles indicate a 29% relapse risk during the early periods of pregnancy for women previously on fingolimod.[4] This patient's attack was significantly worse than her last relapse, affecting her mobility, balance, and the ability to walk, resulting in an increase in EDSS and requiring a wheelchair.

There are multiple recommendations that go with the decision of switching from contraindicated DMTs during pregnancy such as fingolimod to another safer DMT before pregnancy.[5] This decision depends on several factors, such as the patient's clinical picture, disease activity, medication tolerance, and side effects. Preconception counselling should also include discussion of alternative DMT options and timing to reduce rebound risk during pregnancy.

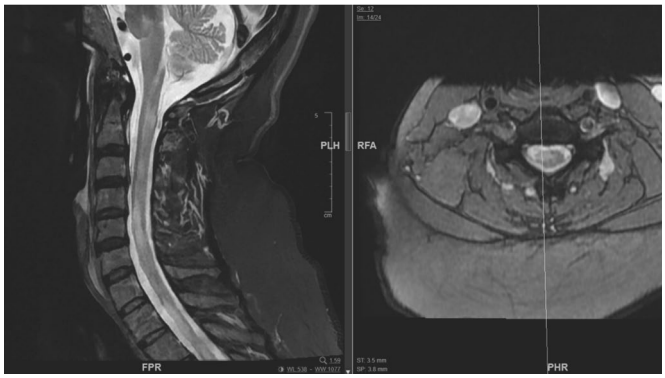

Figure 4. Left image: sagittal cervical MRI of spine STAIR showing multiple abnormal high signal intensities characteristic of MS. Right image: Axial cut of C spine showing MS lesion at the Rt aspect of lateral spine.

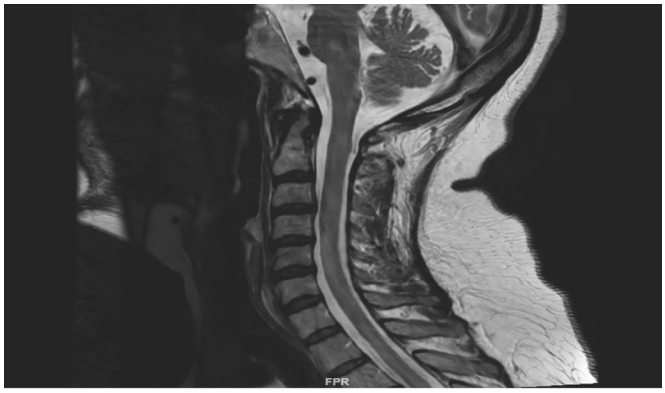

Figure 5. Sagittal cervical MRI of spine T2 showing multiple abnormal high signal intensities characteristic of MS.

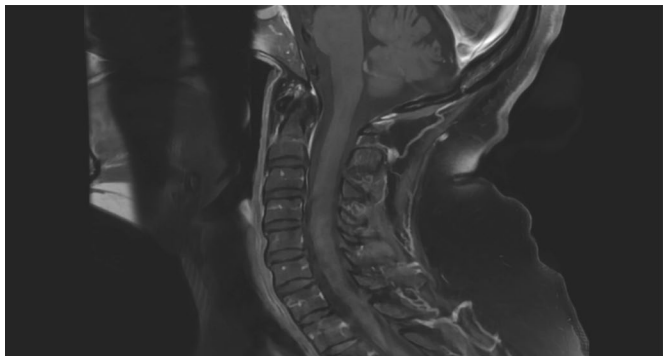

Figure 6. Sagittal cervical MRI of spine T1 with contrast showing multiple abnormal low signal intensities characteristic of old MS with no enhancement.

The escalation to rituximab for managing MS relapses, as in our case, has been reported in various studies, showing better clinical outcomes, in term of EDSS improvement and independency in ambulation, as well as efficacy in reducing and maintaining relapse rates compared to other DMTs. Infants born to treated mothers were healthy, without complications. However, some infants exposed to rituximab in early pregnancy had transient lymphocytopenia after delivery, which normalized 7 months later.[2]

This case report discusses the challenges involved in managing MS rebound during pregnancy, particularly with patients using fingolimod. Despite the belief that pregnancy prevents relapses, severe rebound can occur, demonstrating the importance of early monitoring and intervention to ensure better maternal and fetal outcomes.

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