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RESEARCH

Disease Progression in Pregnant Women with Relapsing–Remitting Multiple Sclerosis Treated with Fingolimod or Natalizumab Prior to Conception: A Systematic Review

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Abstract

Relapsing–remitting multiple sclerosis (RRMS) is the most common inflammatory demyelinating disease of the central nervous system, disproportionately affecting women of childbearing age. This systematic review evaluates the safety and efficacy of two disease-modifying therapies (DMTs), natalizumab and fingolimod, across the preconception, pregnancy, and postpartum periods. Following PRISMA guidelines, we analyzed four observational studies to assess relapse rates and maternal outcomes. Our findings reveal a distinct pattern in disease activity: a reduction in relapses during pregnancy, particularly in the third trimester, followed by a significant surge postpartum. This trend is likely attributable to an immunological shift, marked by a Th2-dominant response, reduced pro-inflammatory cytokines, and increased estrogen and progesterone levels. Notably, patients who had been treated with natalizumab or fingolimod exhibited higher relapse rates compared to those who had used other DMTs. This may reflect a potential selection bias, as these therapies are often prescribed for patients with more severe diseases, who may inherently present with higher relapse rates regardless of treatment discontinuation. Natalizumab continuation into the second trimester is associated with safety and a reduction in relapse risk, whereas fingolimod, due to its teratogenic risk, must be discontinued before conception. Given the inherent postpartum increase in disease activity, individualized care plans and close monitoring are essential. Randomized controlled trials and studies involving larger patient populations are necessary to improve our understanding of the topic and optimize therapeutic approaches, as our conclusions are based solely on observational study data.

Keywords Multiple sclerosis · DMTs · Pregnancy planning · Pregnancy · Postpartum

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Introduction

Multiple sclerosis (MS) is the main demyelinating disorder of the central nervous system. The relapsing–remitting form (RRMS) predominantly affects young women aged 20 to 30, coinciding with their reproductive years [1]. Consequently, pregnancy presents significant challenges for RRMS management, as relapse rates tend to increase during the postpartum period [2, 3].

The systematic exclusion of pregnant women from randomized controlled trials of disease-modifying therapies (DMTs) has resulted in a paucity of reliable data regarding DMT safety and efficacy during pregnancy and the postpartum period [1, 3]. In this context, the use of high-efficacy DMTs such as natalizumab and fingolimod, whose mechanisms of action are illustrated in Fig. 1, may significantly impact relapse rates during these critical periods [3–6].

Given the current lack of consensus on the optimal management strategy for these patients, there is a need to generate scientific evidence. Therefore, the objective of this study is to evaluate whether the use of natalizumab and fingolimod prior to conception influences relapse rates during pregnancy and the postpartum period in women with RRMS.

Methodology

This systematic review was conducted in accordance with PRISMA guidelines. The study protocol was pre-registered in the PROSPERO database under ID: CRD42023453319.

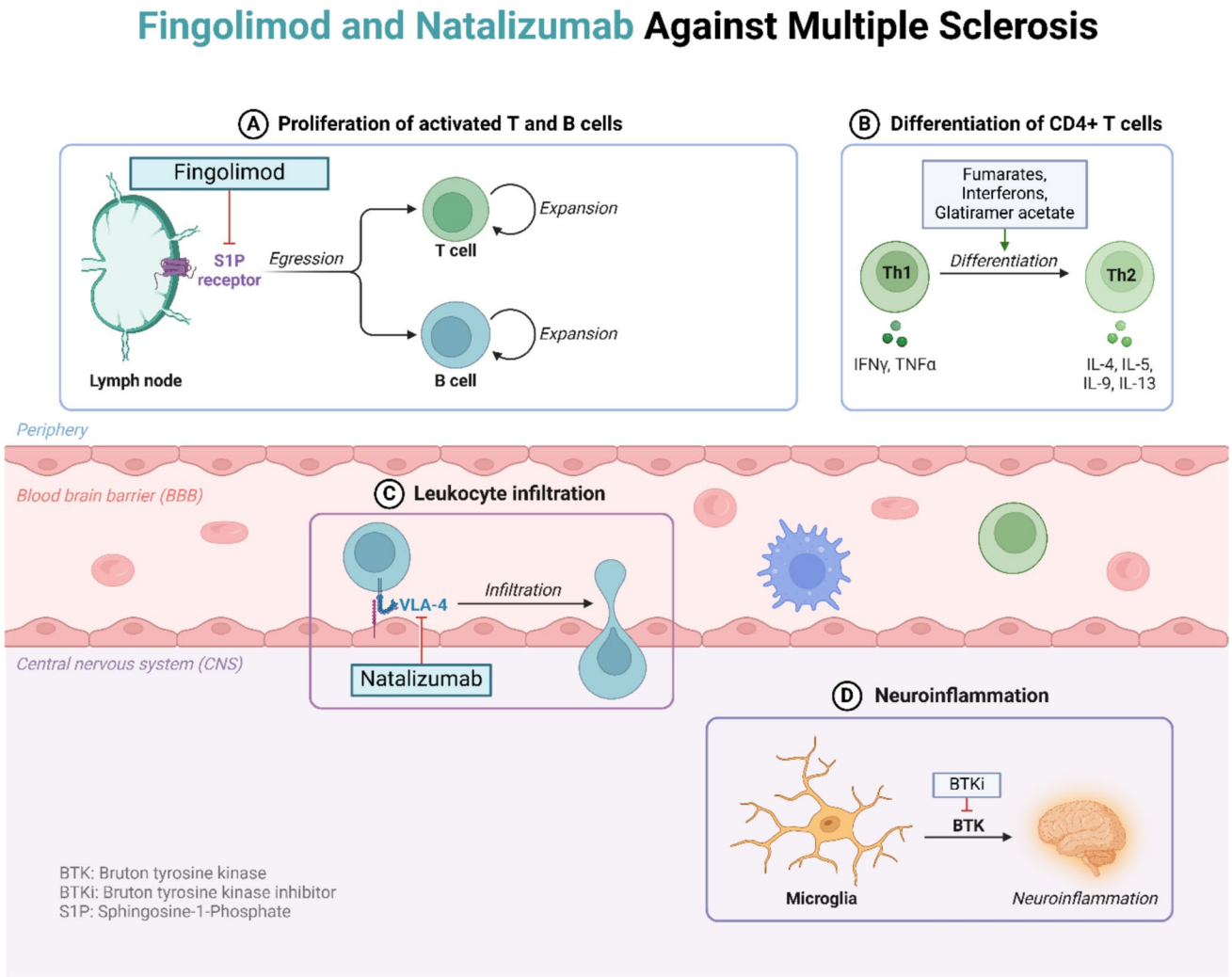

Fig. 1 Fingolimod and natalizumab mechanisms of action. Legend: Fingolimod modulates sphingosine-1 phosphate receptors and natalizumab binds to the alpha chain of the VLA-4 integrin (CD49 d) and is a potent inhibitor of cell migration toward the tissues including CNS [5, 6]. BTK: Bruton tyrosine kinase, BTKi: Bruton tyrosine kinase inhibitor, STP: sphingosine-1-phosphate

Study Selection Criteria

This systematic review aimed to evaluate whether the use of natalizumab and fingolimod prior to conception influences relapse rates during pregnancy and the postpartum period in women with relapsing–remitting multiple sclerosis. Given the limited number of studies specifically addressing this topic, a broad search strategy was adopted to maximize the retrieval of relevant evidence. No restrictions were applied regarding publication date, language, study quality, or sample size to ensure inclusiveness of all potentially informative data. Studies were selected according to the following inclusion criteria:

Study design: Randomized controlled trials and observational controlled studies (cohort and case–control).

Participants: Pregnant women diagnosed with RRMS, with documented use of natalizumab or fingolimod prior to conception and follow-up data available for pregnancy and/or postpartum.

Interventions and comparisons: Use of natalizumab and/or fingolimod prior to pregnancy. Eligible studies included those that compared these agents to other DMTs (e.g., interferon beta, glatiramer acetate, dimethyl fumarate) or to no treatment.

Outcomes: The primary outcome was the number of relapses during pregnancy and the postpartum period. Secondary outcomes included relapse rates in the preconception period and treatment-related adverse events.

Data Sources, Search Strategy, and Extraction

A literature search was conducted using PubMed/MEDLINE, LILACS, and Elsevier databases. The search was structured using Medical Subject Headings (MeSH) keywords. The PubMed/MEDLINE search strategy was as follows:

("Multiple Sclerosis" [MeSH Terms] OR "multiple sclerosis") AND ("Pregnancy" [MeSH Terms] OR "pregnancy" OR "pregnant women") AND ("Natalizumab" [MeSH Terms] OR "natalizumab" OR "Fingolimod Hydrochloride" [MeSH Terms] OR "fingolimod" OR "Disease-Modifying Therapies" OR "DMTs" OR "Immunomodulatory Treatment" OR "Disease-Modifying Drugs").

This strategy was adapted for other databases. In addition, reference lists of all included articles were manually searched to identify any further relevant studies. Informations about searches in other databases and the reasons for excluded studies are available in Supplementary files.

Two independent reviewers screened titles and abstracts to identify potentially eligible studies. Full texts were reviewed for final inclusion based on the eligibility criteria. Disagreements were resolved through discussion; a third reviewer was available but not required. A PRISMA flow diagram was used to depict the study selection process. Study characteristics were summarized in a table, including author, year of publication, population characteristics, interventions, comparators, and outcomes (Table 1).

Quality Assessment and Data Analysis

The quality of observational studies was evaluated using the Newcastle–Ottawa Scale (NOS), which assesses three domains: selection of participants, comparability of study groups, and ascertainment of the exposure or outcome. Each study may receive up to nine stars; higher scores indicate better methodological quality and lower risk of bias [7]. Two reviewers conducted the assessment independently, with discrepancies resolved through consensus.

Although a quantitative synthesis using meta-analysis was initially planned, it was not feasible due to heterogeneity and insufficient numerical data. Attempts to contact study authors for additional information were unsuccessful. Therefore, a descriptive synthesis of the findings was conducted to highlight relevant patterns and inform future investigations.

Results

Screening, Characteristics of the Included Studies, and Assessments of Quality

Four cohort studies were included in this review; no randomized controlled trials (RCTs) were identified. The study selection process is outlined in detail in Fig. 2, while Table 1 provides a summary of key study characteristics, including participant demographics and primary outcomes.

Overall, the studies demonstrate robust methodological quality, featuring clearly defined selection criteria, high comparability between groups, and reliable outcome assessments. This quality is reflected in their high ratings on the Newcastle–Ottawa Scale (NOS). Additional details regarding patient characteristics and NOS evaluations are presented in Tables 2, 3 and 4.

Pre-pregnancy and Pregnancy

In summary, the reviewed studies revealed an overall trend toward an increased number of relapses during pregnancy among patients previously treated with fingolimod or natalizumab compared to the pre-pregnancy period [1–3].

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Table 1 Main characteristics of the included studies

Author	Year	Number of patients	Data source	Inclusion criteria	Exclusion criteria	Objectives
Yeh	2021	1619	MSBase (international online registry)	Women ≥ 18 years with RRMS before conception with at least one visit in the year before and after pregnancy and known pregnancy outcome	Incongruent data, unknown pregnancy outcome and phenotype at conception, and pregnancy occurred before symptom onset and neuromyelitis optical diagnosis	Evaluation of the impact of different DMTs on ARR (annual relapse rate) during pregnancy and postpartum
Berenguer-Ruiz	2019	66	MS clinics in Spain	Women with RRMS diagnosed by McDonald's criteria and were prospectively monitored from the time they expressed a desire for pregnancy	Pregnancy plans that did not result in pregnancy	Evaluation of the impact of discontinuing DMTson ARR in pregnancy
Zanghi	2020	74	MS centers in Italy	Women with a laboratory-supported or clinically established RRMS diagnosis and at least 12 months of postpartum follow-up from three major tertiary MS centers in Italy	Women with MS types other than RRMS and women not receiving treatment at conception, ongoing pregnancies, and abortions	Evaluation of ARR and disease activity during pregnancy and postpartum in MS women treated with different DMTs
Ahmed	2021	93	Data were collected from archived files and a study-specific questionnaire conducted in MS units at three hospitals in Egypt	Clinically definite MS (CDMS) women aged 15–45 with at least one pregnancy in the past 7 years were included in this retrospective observational study	Women with unconfirmed diagnoses or no pregnancies in the past 7 years, those with other demyelinating, vasculitic, or autoimmune diseases, and patients with an EDSS score above 6 at enrollment	Evaluation of ARR in Egyptian women with MS at the time of conception

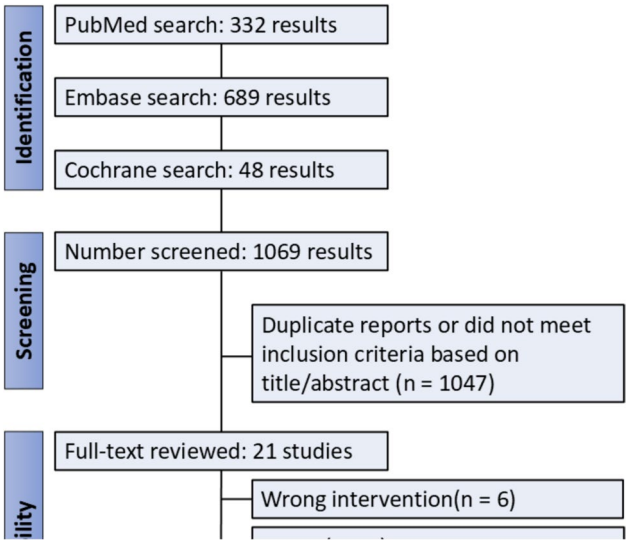

Fig. 2 PRISMA flow diagram of study screening and selection

According to Yeh et al. [1], multivariable analyses identified several independent risk factors for relapses during pregnancy: among them, prior use of natalizumab and fingolimod. Specifically, women receiving fingolimod or natalizumab not only demonstrated a higher ARR relative to those treated with other DMTs before pregnancy but also experienced an escalation in ARR during pregnancy. However, the continued use of natalizumab beyond the first trimester appeared to be protective, with each month of treatment continuation associated with a 24.5% reduction in the odds of relapse, suggesting a potential therapeutic benefit of sustaining this treatment during pregnancy.

Furthermore, Berenguer et al. [2] demonstrated that women on fingolimod or natalizumab had a longer disease duration compared to those receiving interferon-β or glatiramer acetate, despite similar Expanded Disability Status Scale (EDSS) scores. None of the patients in the high-efficacy DMT groups experienced a relapse in the year prior to their baseline assessment; however, during pregnancy, the relapse rate in this subgroup increased to 0.71. Overall, among the patients studied, a total of 11 relapses occurred during pregnancy, 3 in the natalizumab group, 2 in the fingolimod group, and 1 in the interferon-β group. After adjusting for confounders such as the washout period, disease duration, and age at planned pregnancy, the study found that the use of natalizumab or fingolimod was significantly associated with a higher relapse rate compared to interferon-β or glatiramer acetate.

Similarly, in the study by Zanghi et al. [3], differences in disease status prior to pregnancy were observed. Women treated with natalizumab, a subset of whom continued the treatment until the end of the second trimester by mutual agreement with their physicians, had higher EDSS scores during the 12 months preceding conception compared to those on interferons. Within this context, natalizumab emerged as the most frequently utilized DMT among women who experienced relapses during pregnancy. A total of 11 relapses were recorded during gestation, with a notable clustering in the first trimester (one relapse at 8 weeks and six at 12 weeks) and in the third trimester (four relapses between 28 and 34 weeks).

Notably, Ahmed et al. [4] reported a contrast between the number of relapses documented prior to pregnancy and those occurring during pregnancy (84 versus 11 relapses). Within this cohort, eight patients had been inadvertently exposed to fingolimod during the initial months, with treatment being abruptly discontinued thereafter. The remaining cases involved one patient exposed to dimethyl fumarate, another to rituximab, and one patient on interferon-β. The study also noted relapse counts of two, three, and six during the first, second, and third trimesters of gestation, respectively.

Table 2 Informations about patients

Study	Mean age in years	Years of disease duration (median)	EDSS score before pregnancy	Type of DMT used within 1-year prior pregnancy (drug, *n*)
Ahmed [4]	32.74	4.5	(Score, *n*) 0–0.5: 56 1–1.5: 39 2–2.5: 14 3–3.5: 5 ≥ 4: 2	Interferon beta: 39; dimethyl fumarate: 7; natalizumab: 1; rituximab: 9; ocrelizumab: 4; fingolimod: 13; azathioprine: 2
Berenguer-Ruiz [2]	32.1	6.1	(Mean) 1.2	Interferon beta:18; natalizumab: 8; rituximab: 2; glatiramer acetate: 3
Yeh et al. [1]	32	8.9	Not available	Interferon beta: 597; dimethyl fumarate: 57; natalizumab: 219; rituximab: 7; fingolimod: 147; glatiramer acetate: 238; alemtuzumab: 15; azathioprine: 6
Zanghi et al. [3]	36.2	7.5	(Mean, amplitude) 2.0 (1.0–3.5)	Interferon beta: 40; dimethyl fumarate: 4; natalizumab: 27; fingolimod: 4; glatiramer acetate: 5

Table 3 Newcastle–Ottawa assessment

Study	Selection				Comparability	Outcome			Total
	1	2	3	4	5	6	7	8	
Yeh (2021)	★	★	★	Not apply	★★	★	★	★	8
Berenguer-Ruiz (2019)	★	★	★	Not apply	★★	★	★	★	8
Zanghi (2020)	★	★	★	Not apply	★★	★	★	★	8
Ahmed (2021)	★	★	★	Not apply	★★	★	★	★	8

Legend: 1: representation of the exposed cohort; 2: selection of the non-exposed cohort; 3: ascertainment of exposure; 4: the outcome of interest was not present at the start of the study; 5: comparability of cohorts based on the design or analysis; 6: assessment of outcome; 7: was follow-up long enough for outcomes to occur; 8: adequacy of follow-up of cohorts

Postpartum Period

Following delivery, all studies demonstrated a tendency toward an increased frequency of relapses during the postpartum period [1–4]. Yeh et al. [1] indicated that the preconception use of natalizumab, dimethyl fumarate, or the absence of any DMT was associated with a higher hazard of relapse compared to the use of lower-efficacy treatments, even after adjusting for relevant covariates. In contrast, reinitiating high-efficacy therapies postpartum proved to be independently protective, reducing the hazard of relapse by 88.9% compared to those who did not resume treatment. Additionally, breastfeeding was identified as a factor associated with a lower likelihood of relapse.

A regression analysis corroborated these findings, showing that exclusive breastfeeding was linked to a decreased risk of postpartum relapses, whereas nonexclusive breastfeeding did not exhibit the same protective effect. Furthermore, this study

Table 4 Outcomes

Yeh (2021)			
Drug	**ARR amplitude (1 to 12 months before conception)**	**ARR (first trimester, second trimester, third trimester)**	**ARR amplitude (1 to 12 months after pregnancy)**
Natalizumab	0.21–0.39	0.29, 0.47, 0.48	0.35–0.92
Fingolimod	0.35–0.46	0.66, 0.73, 0.39	0.30–0.97
Other DMT	0.15–0.38	0.16–0.34, 0.10–0.17, 0.12–0.14 (amplitude)	0.49–0.82
None DMT	0.24–0.31	0.142, 0.143, 0.146	0.35–0.53
Berenguer (2019)			
Drug	**ARR in the year preceding basal visit**	**ARR during pregnancy**	**ARR after pregnancy**
Natalizumab	0	0.71	NA
Fingolimod	0		NA
Other DMT (glatiramer acetate and IFN-β)	0.11	0.02	NA
Zanghi (2020)			
Drugs	N. of relapses (n. of women) 12 months before pregnancy	Relapses during pregnancy *n* (n. of women)	Relapses during postpartum *n* (n. of women)
Natalizumab	4 (3)	6 (6)	3 (3)
Fingolimod	1 (1)	2 (2)	2 (2)
Other DMT	17 (17)	3 (3)	8 (8)
Ahmed (2021)			
Drugs	Total number of relapses	During pregnancy (relapses)	Postpartum relapses
Natalizumab	84	0	Months 1–3: 8
Fingolimod		8	Months 4–6: 11
Other DMT		3	Months 7–9: 11 Months 10–12: 7

demonstrated a notable increase in the number of relapses during the postpartum period, with the peak incidence occurring between 4 and 9 months after delivery [4].

In line with these observations, Zanghi et al. [3] reported a total of 14 relapses during the postpartum period. Of these, 11 occurred within 4–8 weeks postpartum and three between 10 and 12 weeks, with interferons remaining the most prescribed DMT among those experiencing relapses after delivery. Also, in Berenguer et al. [2], four patients experienced relapses within the first postpartum trimester, with three of these patients having not yet resumed their DMT at the time of relapse.

Discussion

Disease Management and Relapse Trends During Pregnancy

Multiple sclerosis primarily affects women in their 20 s and 30 s, which makes reproductive planning a crucial component of managing the disease. Women with MS face the challenging decision of whether to continue or discontinue DMT before conception. Because current evidence on the safety of DMTs during pregnancy remains limited, clinicians often recommend discontinuation. However, stopping high-efficacy treatments is associated with increased relapse rates, heightened disease activity, and accelerated disability progression [1, 2].

Clinicians have significantly evolved the management of MS during pregnancy since the first major cohort study in 1995. Advances in therapeutics and an expanding body of evidence regarding DMTs have enabled shorter washout periods and reduced ARR prior to conception. For example, Yeh et al. [1] documented a steady decline in ARR from 2005 to 2011 [1, 3]. Although earlier studies focused primarily on patients receiving low-efficacy or no DMTs, more recent research shows that women on high-efficacy treatments experience distinct patterns of pregnancy-related disease activity. In this context, patients treated with natalizumab or fingolimod exhibit higher relapse rates during pregnancy than those on lower-efficacy therapies or no treatment, even after adjusting for confounding factors such as maternal age, washout duration, and disease duration. Notably, discontinuing natalizumab before conception increases relapse risk because it triggers a rebound effect like that observed in nonpregnant MS cohorts. Delaying cessation until later in pregnancy appears to mitigate this risk, and continuing natalizumab beyond the first trimester may even prevent relapses entirely [1, 2].

Nevertheless, clinicians have also reported that exposure to natalizumab late in pregnancy is associated with transient fetal hematologic abnormalities. As a result, some protocols now recommend extended dosing intervals (every 6–8 weeks) until the 32nd–34 th week of gestation. Moreover, cessation of fingolimod often exposes patients to teratogenic risks, including associations with acrania and congenital heart defects, and thus renders fingolimod contraindicated during pregnancy. When continuation is considered, clinicians must implement a careful management plan [8–16].

Emerging evidence further indicates that a higher pre-pregnancy relapse frequency and elevated baseline Expanded Disability Status Scale (EDSS) scores contribute to increased disease activity during pregnancy and poorer postpartum outcomes [4, 5]. For instance, Zanghi et al. [3] reported that women treated with natalizumab registered higher EDSS scores compared to those receiving interferon-based therapies, and Yeh et al. [1] observed that a conception EDSS score ≥ 2 occurred in 35.2% of pregnancies among women on medium- to high-efficacy DMTs versus 21.7% in those on lower-efficacy or no treatment. These findings suggest that the elevated relapse rates in these patients may reflect preexisting severe disease.

Our study also noted a reduction in ARR during pregnancy. Clinicians have long observed that relapse rates decline during pregnancy, reaching their nadir in the third trimester, before increasing postpartum. Although the mechanisms underlying this trend remain incompletely understood, hormonal changes appear to play a key role. Estrogen and other pregnancy-related hormones modulate T- and B-lymphocyte functions and may exert immunomodulatory effects that surpass those of first-line DMTs. Pregnancy induces a shift toward a Th2-biased immune response that maintains fetal tolerance by suppressing pro-inflammatory Th1 cytokines such as interleukin-2 (IL-2), interferon-gamma, and tumor necrosis factor-alpha (TNF-α) [17–22].

Similar immunological shifts manifest in other autoimmune diseases. Studies involving over 500 pregnancies have demonstrated that up to 86% of patients with rheumatoid arthritis experience symptom relief during pregnancy, with improvements beginning in the first trimester and persisting until delivery, although up to 90% encounter disease flares postpartum [23–25]. Moreover, rising levels of estrogen, progesterone, and glucocorticoids during pregnancy promote an anti-inflammatory state: estrogen stimulates IL-10 secretion while suppressing TNF-α production, and progesterone enhances IL-4 and IL-10 levels, further reinforcing the Th2 cytokine profile [26].

Postpartum

Yeh et al. [1] documented a marked increase in disease activity following delivery. They attributed this surge primarily to abrupt hormonal shifts and the reactivation of the immune system. Studies have shown that monocytic IL-12

production increases threefold from the third trimester to postpartum, while TNF-α levels rise by approximately 40%, both of which play crucial roles in reactivating autoimmune processes [27]. Furthermore, diminished hypothalamic secretion of corticotropin-releasing hormone postpartum may contribute to autoimmune flare-ups. Emotional stress and the fatigue associated with newborn care further exacerbate disease activity, underscoring the need for comprehensive psychological and social support during this period [28].

Decisions regarding breastfeeding in MS also present a clinical challenge. Although some investigations have linked lactation to disease exacerbation (potentially due to prolactin's immunostimulatory effects) and even associated prolonged breastfeeding with increased disease severity [29–31], Yeh et al. [1] and Ahmed et al. [4] reported that exclusive breastfeeding appears to exert a protective effect, whereas nonexclusive breastfeeding does not provide similar benefits.

Limitations

It is important to emphasize that our paper has several limitations. First, we included only four retrospective observational studies, and only Yeh et al. [1] enrolled more than 100 participants. Consequently, the smaller cohorts possessed limited statistical power to detect subtle differences in outcomes; moreover, cohorts stratified by medication often differed markedly in size. The included studies also exhibited biases that are typical of observational research. For instance, Ahmed et al. [4] encountered recall bias when collecting data via questionnaires, and studies that extracted data from hospital records or databases may suffer from registry-based limitations.

We also noted a potential selection bias that inflated the ARR during pregnancy among patients using fingolimod and natalizumab. Because these patients exhibited greater baseline disease severity, the observed increase in ARR may partly reflect preexisting differences rather than solely the effects of the therapies.

A further constraint derives from the heterogeneity of the included studies. Variations in DMT protocols and differences in data presentation precluded the performance of a meta-analysis. This limited the generalizability of our findings, as we could not quantitatively synthesize results across studies to draw broader conclusions.

Despite these limitations, our study provides valuable insights into MS management during pregnancy and highlights the scarcity of evidence on this topic. Our findings underscore the necessity for future high-quality clinical studies to address these gaps.

Conclusion

First and foremost, we emphasize that all our findings are based on observational studies. In summary, our study identified a trend in which patients treated with fingolimod and natalizumab experienced a higher number of relapses during pregnancy compared to patients receiving other DMTs. Statistical analyses classified these patients as a high-risk group for relapses during pregnancy. Clinically, these observations underscore the need for more intensive monitoring, greater attention, and individualized clinical planning for this patient population. Importantly, continuing natalizumab into the later stages of pregnancy demonstrated a protective effect, suggesting a potential therapeutic strategy for these women. Additionally, we observed a trend toward reduced relapse rates during pregnancy, likely resulting from the Th1/Th2 immune shift and hormonal influences, findings that may eventually elucidate further aspects of the disease's pathophysiology and suggest new therapeutic targets. In conclusion, our study reveals significant gaps in the literature regarding MS management during pregnancy and encourages the initiation of new, high-quality studies on this subject.

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Data Availability No datasets were generated or analysed during the current study.

Code Availability Not applicable.

Declarations

Ethical Approval Not applicable.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Competing interests The authors declare no competing interests.

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