Multiple sclerosis

Review

Postpartum relapse risk in multiple sclerosis: a systematic review and meta-analysis

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ABSTRACT

The influence of pregnancy on the course of multiple sclerosis (MS) has long been controversial. While historical evidence suggests a substantial decline in relapse rates during pregnancy followed by a rebound in the postpartum period, more recent work yielded equivocal results. We performed a systematic review and meta-analysis on data from cohort studies to determine whether women with MS experience increased relapse rates after delivery. A systematic literature search was conducted in the databases MEDLINE and Epistemonikos on the topic 'motherhood choice in MS' in March 2022. We included cohort studies assessing the association between pregnancy and MS relapse activity defined by the annualised relapse rate after 3, 6, 9 and 12 months post partum. Furthermore, information about disease-modifying therapies (DMT) and breast feeding was considered, if available. 5369 publications were identified. Of these, 93 full-text articles on MS relapse activity during the postpartum period were screened. 11 studies including 2739 pregnancies were eligible. Women with MS showed a significantly increased relapse rate in the first 6 months post partum, compared with preconception with the incidence rate ratio (IRR) almost doubled in the first 3 months post partum (1.87, 95% CI 1.40 to 2.50). However, at 10–12 months post partum, the IRR decreased significantly (0.81, 95% CI 0.67 to 0.98). Subanalysis on influencing parameters suggested that preconceptional DMTs (IRR for highly-effective DMTs 2.76, 95% CI 1.34 to 5.69) and exclusive breast feeding (risk ratio 0.39, 95% CI 0.13 to 0.86) significantly influenced postpartum relapse risk. Increased postpartum annualised relapse rate and possible modifiers should be considered in counselling women with MS who are considering pregnancy.

INTRODUCTION

Background

Multiple sclerosis (MS) is a chronic inflammatory and degenerative disorder of the central nervous system. Worldwide more than 2.8 million people are diagnosed with MS, with a female to male ratio of almost 3:1.1–2 Around 85% of people with MS have a relapsing-remitting disease (RRMS) at onset, characterised by acute or subacute neurological deficits (relapses) followed by complete or incomplete recovery. As MS most often manifests below the age of 40, pregnancy is an important issue for women with MS (wwMS). Until the end of the 1990s, women diagnosed with MS were often advised not to get pregnant.3 Fertility does not seem to be relevantly compromised in wwMS,4 their reproductive rate is lower compared with healthy women, possibly reflecting uncertainties and worries around the topic of pregnancy that MS may be experiencing.5–6 While evidence from the last 20 years indicates that inflammatory disease activity is substantially reduced during pregnancy, the effect on postpartum risk for rebound disease activity is less clear.7

Pathophysiologically, a reduction in the relapse rate during pregnancy and an increase after childbirth are consistent with the immunological and hormonal changes occurring during pregnancy.3 However, one of the most recent cohort studies on postpartum disease activity and pregnancy is in contrast to the earlier reports.9 This could—at least in part—be linked to substantial changes that have occurred in the epidemiology, severity of MS and the therapeutic landscape over recent years.10–12 This reasoned to question whether patients with MS still suffer from an increased risk of relapses in the postpartum period. In addition, to our knowledge, no systematic review focused on the evolution of relapse rates post partum up to 1 year.9 10–12

In the present paper, we reviewed the evidence for the influence of pregnancy on the postpartum relapse rate. We performed a systematic review and meta-analysis of cohort studies examining relapse rates within each quarter of the first year post partum. Furthermore, we investigated the effects of preconceptional disease-modifying therapies (DMTs) and breast feeding on the postpartum relapse rate.

METHODS

Data sources and search strategy

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline (online supplemental table 1).13 As this work is part of a larger project and scoping review (‘Motherhood choice in multiple sclerosis and systemic lupus erythematosus – a mixed methods study’) aiming to explore the knowledge as well as information regarding pregnancy to develop a counselling programme for wwMS, we searched the electronic databases MEDLINE and Epistemonikos (from inception to 15 February 2022) on the topic ‘motherhood choice in MS’ with additional backward and forward reference tracking (online supplemental...
tables 2 and 3). The search strategy was set up for a scoping review, and the results on relapses and pregnancy were used for this review. During the full-text screening, all included studies were sorted by topic, using the software Mendeley. For the scoping review, we excluded the following references: (1) commentaries or letters to the editor; (2) reviews about MS without a focus on pregnancy or motherhood; (3) publications on general risk factors of MS; (4) publications in languages other than English or German; (5) studies about neuromyelitis optica spectrum disorder; (6) case reports with less than five patients; (7) randomised controlled trials with the specification ‘pregnant women were/were excluded’; (8) effects of pregnancy on the immune system without linkage to disease-specific data on MS; and (9) animal or cell studies. Two researchers screened titles and abstracts of the studies independently using the online software Rayyan. Discrepancies were resolved by discussion.

For this review, we considered all studies on the topic ‘influence of pregnancy on the relapse rate’. We included studies that met all of the following criteria: (1) cohort study; (2) sample with ≥30 wwMS; (3) ≥80% wwMS having RRMS; (4) information on pre-pregnancy annualised relapse rate (ARR); (5) data on the ARR ≥3 months post partum; (6) MS diagnosed before pregnancy; and (7) information on DMT received before or during pregnancy. We only included studies with information on relapses from the whole pregnancy period and at least the first 3 months after delivery. For the meta-analysis, only cohort studies were included which met the eligibility criteria and our defined quality requirements described below.

Quality assessment
Two researchers independently assessed the quality of cohort studies using the CASP (Critical Appraisal Skills Programme) tool for cohort studies. Specifically, they rated the recruitment process, relapse definition, methodology for assessing relapses, follow-up, completeness of clinical characteristics (age at conception, Expanded Disability Status Scale (EDSS), disease duration, breast feeding) and precision estimates (CIs). Discrepancies were resolved by discussion. Studies rated to have highly selective recruitment or inaccurate definition of relapses (eg, only based on corticosteroid prescription) were excluded from the meta-analysis.

Outcome data extraction and synthesis
Our primary outcome was the ARR of the first 3 months post partum compared with the pre-pregnancy period. We also considered the ARR of all subsequent quarters of the first year post partum. We compared the ARR for 12 months preconception versus 0–3 months, 4–6 months, 7–9 months, 10–12 months and 0–12 months post partum. The possible influence of DMTs or breast feeding on relapse rate was examined in subgroup analyses.

Statistical analysis
The log rate ratios of the ARR of the different time periods were combined in random-effects meta-analyses using the inverse variance method. Our null hypothesis was that there is no difference between pre-pregnancy and post-pregnancy rates, that is, incidence RR (IRR) equal to 1. Estimates of RR were reported with 95% CIs and p values. The results are displayed as forest plots facilitating visual inspection of between-study heterogeneity. Furthermore, between-study heterogeneity was evaluated by calculating tau² and I² and the χ² test of heterogeneity. Significant heterogeneity was further examined in sensitivity analyses.

Information on a possible association between the amount of patients treated with DMTs or the amount of patients breast feeding and the postpartum relapse rate was analysed in a linear regression model and presented in a scatter plot. Only a few studies reported data on risk ratios of individual DMTs. We examined the effect of highly-effective DMTs (H-DMTs, including natalizumab, alemtuzumab or CD20-therapy such as rituximab, ocrelizumab) on relapse RR and displayed them with forest plots. As previous studies discussed the protective effect of exclusive breast feeding on relapse rate, we searched for information about exclusive breast feeding in cohort studies included in this review. However, exclusive breast feeding was only reported in a minority of studies. Risk ratios were analysed in the following groups: exclusive breast feeding, non-exclusive breast feeding and no breast feeding.

The meta-analyses were conducted using the RevMan V.5.4 software and R V.4.2.1 software.

RESULTS
Of the 5369 publications identified in the scoping review search, 274 were removed before screening as duplicates (figure 1). Of the remaining 5095 references, 93 full-text articles were assigned to the specific term ‘influence of pregnancy on the relapse rate’ during screening. Sixty-five studies were excluded according to the eligibility criteria of the systematic review and meta-analysis (24 were not cohort studies, 37 had incomplete data and 4 included <30 wwMS). Eleven additional studies were excluded due to possible cohort overlap, and six after quality assessment due to unacceptable study recruitment (not all patients of a cohort in a retrospective analysis or not a prospective consecutive approach), implausible data (eg, >3 relapses per trimester) or lack of relapse definition. When sample overlap between different publications using the same national cohort could have occurred, we decided to include the largest study. In total, 11 studies with 2739 pregnancies were included in the systematic review and meta-analysis (figure 1).

The quality assessment showed heterogeneity in study design, conduct and reporting (figure 2A; online supplemental table 4). Only in seven studies, recruitment was performed rigorously by evaluating consecutive prospective or retrospective cohorts including all patients fulfilling selection criteria in a given time frame to minimise selection bias. Four studies lacked information on dropouts or showed dropout rates >10% without reporting reasons. In four publications possible variables of interest such as DMT and breast feeding, which can influence the result of postpartum relapse rate, were not or not sufficiently identified. In four studies these variables were not or not sufficiently taken into account. Only one study met all quality criteria. Six studies were excluded because of selective recruitment and/or inaccurate relapse assessment or definition. The quality assessment is visualised by a radar chart (figure 2B).

In the 11 studies included in the meta-analyses, the mean age at conception ranged from 30 to 36 years, the mean disease duration from 5 to 9 years and the mean EDSS score at baseline ranged from 1.0 to 2.0. Pre-pregnancy observation periods were 1 or 2 years, postpartum follow-up varied between studies from 3 months to 2 years after delivery. The included studies and the patient characteristics are presented in more detail in online supplemental tables 5 and 6.
Eight studies estimated the ARR within the whole postpartum year, including the newest cohorts. In seven studies, data were available to calculate the ARR for the whole year as an average of the ARRs of the four postpartum quarters. Taking all 11 studies together, results suggest that ARR was higher in the first 3 months after delivery compared...
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with the pre-pregnancy period (IRR 1.87, 95% CI 1.40 to 2.50; p<0.0001) (figure 3A). Among the studies included, the study of Langer-Gould et al detected an IRR below 1. A substantial between-trial heterogeneity was observed (tau^2=0.19, I^2=82%, p<0.00001). Our results suggest that relapse decreased after the second postpartum quarter onwards, reaching the lowest value in the fourth quarter (months 10–12 post partum: IRR 0.81, 95% CI 0.67 to 0.98; p=0.03) (figure 3A–D). Looking at the whole postpartum year, the results indicate that ARR was higher (IRR 1.29, 95% CI 1.08 to 1.54; p=0.004) in the year after delivery compared with the pre-pregnancy year (figure 3E). Between-trial heterogeneity was estimated as moderate (tau^2=0.04, I^2=73%, p=0.0006). The mean pre-pregnancy ARR was 0.36 (0.04–0.82). We conducted a sensitivity analysis for the first 3 months and 4–6 months post partum with seven cohort studies providing data up to 1 year. IRR was 1.65 at 0–3 months post partum (95%CI 1.15 to 2.25) and 1.29 at 4–6 months post partum (95%CI 1.08 to 1.53). This goes in line with the main results. The sensitivity analysis of this subgroup is summarised in figure 3F.7 23 24 35–38

To explore between-study heterogeneity, we conducted further sensitivity analyses for the first 3-month period after delivery. By excluding the three studies with SE >0.3, the betwee-study heterogeneity could be reduced slightly (online supplemental figure 1A). A reduction of tau^2 from 0.19 to 0.11 was achieved by excluding the only study with a log RR below 0 (online supplemental figure 1B). When combining both steps, a between-study heterogeneity (tau^2) of 0 (and consequently an I^2 of 0%) was obtained, while the resulting CI (95% CI 1.40 to 2.50) supporting the original conclusions (online supplemental figure 1C).

H-DMTs are associated with an increased postpartum relapse rate

Linear regression of the IRRs and the percentages of patients treated with DMT before pregnancy in the cohorts showed a trend but no significant association (F(1, 8)=4.647; p=0.06; figure 4A) with the postpartum relapse rate. The only study without DMT use is the oldest; in all other studies, at least 22% of women received DMTs before pregnancy. As a second step, we performed a subgroup analysis of cohorts referring to H-DMTs. In three studies all patients or a subgroup of patients were treated with natalizumab,22 41 42 in Razaz et al subgroup analyses were performed in patients treated with natalizumab or rituximab.37 The results suggest that in patients receiving H-DMTs, the ARR was more than twofold increased in the first 3 months post partum in comparison to preconception (IRR 2.76; 95% CI 1.34 to 5.69, p=0.006) (figure 4B). Even when excluding the small cohort of Alroughani et al (IRR 2.31; 95% CI 1.23 to 4.34, p=0.009), which included only 24 pregnancies, the RRs remained increased (online supplemental figure 2). Further stratification of the analysis on individual DMTs taken by the patients in the preconception period was not applicable due to a lack of information.

Exclusive breastfeeding indicates an association with a reduced postpartum relapse rate

We analysed the ARR in a subgroup of cohorts where information was available on the status of nursing in the first month post partum. In eight studies information was given.7 23 24 36 38–40 42

The results indicate that cohorts with a high percentage of breastfeeding women did not have a significant reduction in postpartum relapse risk compared with cohorts with fewer breastfeeding
women ($F(1, 6) = 1.164; \ p = 0.3220$; figure 4C). The IRR comparing the first 3 months with the 12 months preconception is comparable to the main group (IRR 1.74, 95% CI 1.23 to 2.48, $p = 0.002$). However, the duration of breast feeding and the exclusiveness of breast feeding was not calculated in these studies. Percentages of exclusive breast feeding ranged between 31% and 46% in the four studies in which this information was available.\(^7\)\(^-\)\(^24\) We included three studies with n=398, 496 and 243 pregnancies where information on breast feeding (exclusively for at least 2 months, non-exclusively and not at all) was available to perform risk ratio analysis.\(^7\)\(^-\)\(^24\) Our results indicate that patients who exclusive breast fed had a lower relapse risk in the first 6 months post partum compared with those who did not breast feed (risk ratio 0.39, 95%CI 0.18 to 0.86; $p = 0.02$; figure 4D). The relapse risk in exclusively breastfeeding women also seemed to be lower compared with non-exclusively breastfeeding women (risk ratio 0.55, 95%CI 0.31 to 0.97; $p = 0.04$; online supplemental figure 3).

**DISCUSSION**

In this systematic review and meta-analysis, we assessed the postpartum relapse rate of patients in MS and could confirm an increased relapse risk at 3 and 6 months after delivery in comparison to the pre-pregnancy period (including in studies of recent cohorts). However, it also seems that in the following months post partum, the relapse rate decreases and reaches pre-pregnancy activity at 7–9 months post partum. The use of higher efficient DMTs was associated with a more than doubled relapse risk, while exclusively breast feeding was associated with a reduced postpartum relapse risk ratio.

Our systematic literature search yielded three previous meta-analyses on the effects of pregnancy on the disease course, conducted by Finkelsztejn et al, Dobson et al and Modrego et al.\(^9\)\(^-\)\(^13\)\(^-\)\(^44\) All meta-analyses included studies of heterogenous quality, possible overlapping cohorts and studies with small sample sizes without standardised quality assessment. In contrast to our analysis, Finkelsztejn et al did not examine the four-quarters of the postpartum year separately. Instead, the calculated relapse rate (ARR 0.758; 95%CI 0.64 to 0.87) results from studies in which the period of observation varied from 3 to 12 months after delivery.\(^9\) In the meta-analysis of Dobson et al, results of the postpartum period should be taken with caution as the studies analysed are highly heterogeneous.\(^44\) In Modrego et al inclusion and exclusion criteria for the paper included in the meta-analysis are not stated and a study flow diagram is not given.\(^13\)

The ARR observed by Langer-Gould et al differs substantially from that in all other studies of our meta-analysis and especially also from most recent cohorts. This can be due to differences in study design or the patient cohorts. In fact, the study published by Langer-Gould et al is the only population-based study. All other studies included in the review were referral centre studies. In the study by Langer-Gould et al, data were extracted from electronic health records, which might have led to an under-reporting of mild relapses, because not all women were seen by a neurologist, potentially leading to relevant differences in the detection of clinical events. Furthermore, different to most other studies the observation period covered 2 years before gestation in this study and relapse qualification required that symptoms lasted for at least 48 hours (instead of 24 hours). In addition, a proportion of 16% of women was diagnosed with clinically isolated syndrome or had their symptom onset during pregnancy. However, disease duration alone seems not to be the influencing factor affecting the relapse rate. In two other cohorts,\(^36\)\(^-\)\(^38\) of our meta-analysis presenting an increase in postpartum relapse rate...
of 0.37 vs 0.36). Thus, the low ratio post partum seen by Langer-Gould was comparable to the mean of all included cohort studies (ARR in the pre-
gould feeding on relapse risk. Additional independent cohort data are needed to clarify the postulated effect of breast feeding on relapse risk.

The results of our meta-analysis show a large between-study heterogeneity of findings for the first and fourth trimesters as well as for the entire postpartum year. Besides differences in the number of women who breast fed and received therapy, this is presumably due to methodological differences between the studies. Here a main confounding factor could be the ascertainment of relapses. Most studies collected at least the relapse rate before pregnancy retrospectively. Variation in relapse definition might be another source of bias. Most studies defined a relapse as the appearance of neurological dysfunction lasting longer than 24 hours.23 24 37 42 In the most rigorous study, neurological symptoms had to persist for at least 48 hours to be considered a relapse.7 Potentially, some similar events that were counted as relapses in older studies might therefore not have been qualified here.

Family planning in wwMS requires careful consideration, especially because many DMTs are contraindicated during pregnancy. The choice for DMT in wwMS with childbearing preferences, among others, depends on the disease activity, the safety of the drug and the administration. Interferons and glatiramer acetate are considered not to change the risk of abortions, malformations or low birth weight of the newborn.46 Regarding the treatment of highly active MS, there is increasing knowledge about the long-term maternal and infant outcomes for highly effective drugs such as natalizumab.46 Our subgroup analysis of patients treated with H-DMT suggested a higher postpartum relapse risk compared with the main group. If this increase in postpartum relapse rate is caused by the high disease activity in these patients per se or due to the timing of discontinuation of natalizumab before or during pregnancy remains an open question. A rebound of disease activity after discontinuation of natalizumab treatment has been described outside the setting of pregnancy.47 48 In 2018, the anti-CD20 therapy ocrelizumab was approved. According to Razaz et al, anti-CD20 treated patients did not exhibit an increased risk of postpartum relapse rate.39 However, results are limited due to low patient numbers and heterogeneity. Rituximab was suspended on average 104±43 days before conception. First data about safety during pregnancy and breast feeding suggest no increased fetal or newborn risk in ocrelizumab as well as alemtuzumab.48 49 Among women treated with alemtuzumab a minimal increase in ARR occurred in the first 3 months post partum.39 To better understand the effect of switching on and of DMTs during pregnancy, registries with wwMS such as the German Multiple Sclerosis and Pregnancy Registry are highly needed.51

It is generally known that breast feeding has a positive effect on the child’s health.52 Unfortunately, information about exclusiveness and duration of breast feeding was only given in a few of the studies included in our analysis. While we could not detect a significant correlation of the proportion of patients who were breast feeding with the relapse RR post partum, analysing the possible beneficial effect of exclusive breast feeding in a subgroup of recently published cohort studies confirmed a risk reduction in postpartum relapse rate.7 24 38 This is in line with a meta-analysis not including two of the recent studies reporting a 43% reduced risk of postpartum relapses in women who breast fed.53 The benefit was stronger for exclusive breast feeding, but the correlation was also apparent when comparing non-exclusive breastfeeding to non-breastfeeding patients. A potential favourable influence of breast feeding could be mediated by immunological mechanisms related to lactational amenorrhoea.21 This effect may be confounded by the fact that women with a more benign MS are more likely to breast feed, while women with a high ARR before pregnancy tend to resume DMTs early after delivery (‘reverse causality’). However, after adjusting for the preconceptional relapse rate, Krysko et al concluded that the benefit cannot be explained by this factor alone.55 Overall, the impact of breast feeding on relapse rate and the general health benefit of breast feeding for mother and child have to be weighed up. Restrictions of DMTs during breast feeding are mainly based on the limited available information about the potential transfer of DMTs into breast milk and possible toxic effects on the child.54 Commonly, women with MS face the difficult challenge of choosing between breast feeding and DMT resumption. Further biological evaluations and clinical observations are required to prove the safety of the combination of DMTs and breast feeding.

Strength and limitations

Studies included in our meta-analysis investigated the disease course in cohorts from eight different countries. These cross-national data make our findings highly reliable and transferable to other patient populations. The robust methodology with vigorous screening and quality criteria is a strength of this review. Concurrently, establishing quality-oriented eligibility criteria enabled a selection of larger cohort studies of high quality, but led to a lower number of selected studies for the meta-analysis in the end. Additionally, deciding against possible overlapping cohorts such as MSBase-related cohorts contributed to this effect. A lower number of studies leads to a bigger weight for every cohort in the analysis and consecutively a possible bias if one or some studies differ substantially from the rest. This could have been relevant for more selective studies like the cohort published by Hellwig et al, which reports exclusively on patients treated with natalizumab.38 However, the sensitivity analyses confirmed the consistency of our overall results even when excluding some cohort studies.

The eligible cohort studies showed relevant limitations concerning the information given. Missing information included the documentation of dropout rates, lacking analysis of confounders, here, especially the timing of the DMTs, the information on breast feeding or even its exclusiveness in many cohort studies. Due to the incomplete information on DMT use, especially single DMTs use and timing in some of the cohorts, this review is not able to conclude about the influence of the DMT used before and during pregnancy and the postpartum relapse rate. Further studies have to specify the possible impact of DMT timing or discontinuation on the relapse rate post partum. Overall, as in many meta-analyses, the biggest limitation is that we did not have access to individual participant data. In particular, regarding DMTs and breast feeding, it would be much more informative than the aggregated data we used. Registries and prospective studies have to complement our findings on DMTs and breast feeding in the future.
CONCLUSION
Our results suggest that the postpartum relapse risk in MS is increased during the first and second postpartum trimesters and declines until the fourth 3-months-period post partum. According to this data, DMT exposure before or during pregnancy is not associated with a reduction of this phenomenon. However, exclusive breast feeding seems to be associated with a beneficial effect on the postpartum relapse rate. The need to restart maternal treatment with DMTs on the one hand and the wish to breast feed on the other, leads to a decisive dilemma which needs highly competent counselling. Future studies should aim for safety analyses of new and known DMTs during breast feeding to combine the most effective strategies to reduce the postpartum relapse rate.

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Acknowledgements We thank all authors of published studies mentioned in this paper who provided information and even data from their cohort studies.

Contributors CS and LS contributed equally to this paper. CS, LS, ACR and CH conceptualised the review and meta-analysis, drafted and edited the protocol. CS, LS, JP, CR, ACR and CH performed literature screening, quality assessment and data extraction. CS, LS, JP, ACR and CH performed the data analysis. CS, LS, JP, KH, CR, AS, AG, SMG, SK, TF, CH and ACR reviewed, edited and approved the review before publication.

Funding This project was funded by the Deutsche Forschungsgemeinschaft (DFG) (RA 3296/1-1 and GO 1357/8-2, KFO 296). CR was supported by the Forschungsförderungsfond der Medizinischen Fakultät, Universitätsklinikum Hamburg-Eppendorf.

Competing interests AG, ACR, CR, JP and LS have nothing to declare. KH reports research support and speaker honoraria from Biogen, Bayer Healthcare, Novartis Pharma, Teva, Sanofi Genzyme, Merck Serono and Roche. SMG reports honoraria from Mylan GmbH, Almirall SA. C. and Cellenge and research grants from Biogen, outside the submitted work. He receives research funding from the Deutscher Forschungsgemeinschaft, Bundesministerium für Bildung und Forschung, Bundesministerium für Gesundheit, the National MS Society and the European Kommissions-Hamburg-Eppendorf.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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