**Change in pregnancy-associated multiple sclerosis relapse rates over time: a meta-analysis**

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**Abstract**

**Background:** Women with MS are advised that relapse rates fall during pregnancy and rebound post-partum. This advice originates from 1998; smaller, more recent, studies have not been previously pooled.

**Methods:** All studies published since 1998 providing raw relapse data were considered for inclusion. Single arm meta-analysis was performed using a restricted maximum likelihood random effects model with inverse variance; secondary subgroup analysis and meta regression were then performed. Annualised relapse rates (ARR), or relapse numbers/rates suitable for conversion into ARR during pregnancy and the post-partum period were included. Secondary subgroup analysis examined year of data collection, DMT exposure, breastfeeding and data source.

**Results:** 7034 pregnancies from 6430 women were included. ARR fell from 0.57 (95%CI 0.45-0.70) pre-pregnancy to 0.36 (0.28-0.44), 0.29 (0.21-0.36) and 0.16 (0.11-0.21) during trimesters 1,2, and 3, with a post-partum rebound (ARR 0.85, 95%CI 0.70-1.00). ARR reduced pre-pregnancy and post-partum over time (p<0.001). Relapse rates were lower in claims databases than elsewhere.

**Conclusions:** Despite high heterogeneity, we confirm the historic assumption that ARR reduces during pregnancy, and demonstrate an overall reduction in ARR over time. Studies using data originating from claims databases demonstrated a lower relapse rate at all time points, which has not previously been demonstrated.

**Introduction**

Multiple sclerosis is most commonly diagnosed in young women - 70% of people with MS are female, and the mean age of onset is 32 [[1]](https://paperpile.com/c/WIATem/SbYHx). Most are diagnosed with relapsing-remitting MS. The accepted dogma is that overall relapse rates fall during pregnancy, with a post-partum rebound in disease activity [[2]](https://paperpile.com/c/WIATem/6gzQ); however this is based on data drawn from an untreated natural history cohort with active disease.

Evolving MS diagnostic criteria [[3]](https://paperpile.com/c/WIATem/Efai) mean that individuals who did not meet diagnostic criteria 20 years ago are now diagnosed with MS and offered disease modifying treatment (DMT). Historically women with MS were advised to defer treatment until they had completed their families. The increasing realisation that early effective treatment has potential long-term benefits [[4]](https://paperpile.com/c/WIATem/YElrR) means that more people with MS start DMT soon after diagnosis. Concerns regarding the safety of DMT in pregnancy have led to women with MS being counselled to stop DMT for weeks or months prior to trying to conceive. Similarly, women have faced a choice between early resumption of DMT post-partum or breastfeeding, with the two seen as mutually exclusive.

More recent research has focused on the influence of DMT cessation, washout, and re-commencement on both disease activity/relapse rates and neonatal outcomes, along with attempts to assess the impact of breast-feeding on post-partum MS disease activity. There have been few attempts to integrate the data evolving from these more modern cohorts [[5]](https://paperpile.com/c/WIATem/997I) [[6]](https://paperpile.com/c/WIATem/sy62)[[7]](https://paperpile.com/c/WIATem/1FID). Evolving diagnosis and treatment considerations in MS continue to pose challenges for patient management in relation to family planning.

In this meta-analysis we set out to establish the pattern of relapse rates in women with MS during pregnancy, examine if and how this has changed over the past 20 years, and explore possible reasons for any changes observed.

**Methods**

*Data extraction and quality assessment*

Pubmed (including Medline), Embase and the Cochrane database were searched using the terms “multiple sclerosis” and “pregnancy” with publication year 1998 or later. Reference lists of review articles were perused, and experts in the field were consulted. Quality was assessed using a modified version of the Newcastle-Ottowa scale [[8]](https://paperpile.com/c/WIATem/5hJ1).

Studies with a publication date of 1998 (the year of PRIMS publication [[2]](https://paperpile.com/c/WIATem/6gzQ)) to present were considered for inclusion. Studies were considered if they contained information on a minimum of 20 MS pregnancies in order to mitigate bias resulting from small case series. Studies where individual women had >1 pregnancy were included, with each pregnancy counted as an independent event [[9]](https://paperpile.com/c/WIATem/Wndf). Clinical trials examining the potential effect of immunomodulators on post-partum relapse rates were excluded. Both prospective and retrospective cohorts were considered for inclusion. Studies were suitable for inclusion if they gave either raw relapse data, annualised relapse rates (ARR), or relapse numbers/rates suitable for conversion into ARR using standard formuale, for at least one of:

 i. Baseline pre-pregnancy relapse rates over a minimum 3 months to maximum 24 months prior to pregnancy

 ii. Trimesters 1,2, and/or 3 of pregnancy

 iii. Entire pregnancy (9 months)

 iv. 3 or 12 months post-partum

Studies were not required to provide data on either DMT use or breastfeeding in order to be included; however where this was provided it was recorded. Where data were given by subgroup (e.g. by DMT exposure at a particular time point, or breastfeeding behaviour) these were recorded as separate cohorts. Cohorts within papers were cross-referenced, and where overlapping the latest (most recent, and largest) cohort was included in the analysis.

The original data source used was recorded, and classified as one of 3 types – MS database (i.e. a database including all MS patients seen in a particular centre or region, from which patients with pregnancy were selected in a post-hoc manner), pregnancy-specific database (i.e. enrolling/including only those patients who are either pregnant or actively express a desire for pregnancy), and claims databases (based on medical insurance claims or coding in medical notes used to bill patients). Where data were taken from alternative sources, such as retrospective questionnaires on a small cohort of patients, these studies were included in the main analysis but excluded from subgroup analyses examining the role of the data source in potentially driving heterogeneity.

Where available, the year(s) of participant enrollment/data collection were recorded from published data, and the mid year of enrollment calculated. Where specified in the manuscript, the MS diagnostic criteria used were recorded. Where multiple diagnostic criteria were used across cohorts, the earliest criteria used were recorded and used for analysis. Where standard error (se) was given this was recorded, alternatively this was calculated from standard deviation or interquartile range using standard formulae.

*Statistical analysis*

Single arm meta-analysis was performed on relapse rate using a restricted maximum likelihood random effects model with inverse variance. Confidence intervals were set at 95%. Study heterogeneity was assessed using I2; bias was assessed using both visual inspection of funnel plots and Egger statistic. ARR was the primary outcome measure.

In order to explore the potential contribution of factors to between-study heterogeneity and/or change over time, pre-specified subgroup analyses were performed. Studies were divided into three subgroups according to the mid-year of data collection: 1994-2004, 2005-2009 and 2009-present; and according to the MS diagnostic criteria used. Random effects meta regression was performed, subgroup comparisons performed using chi square, and I2 was used to assess residual heterogeneity.

Subsequently meta regression was performed on ARR pre-pregnancy and in each trimester of pregnancy according to the proportion of individuals exposed to DMT: (i) at any time in the 2 years prior to pregnancy, and (ii) at the time of conception. Additionally, the effect of (i) DMT exposure in the first 3 months post-partum, and (ii) the proportion of the study population reported to be breastfeeding on post-partum ARR was examined in a similar manner. ARR according to primary data source (as defined above) was also explored. Residual study heterogeneity for each of these analyses was assessed using I2.

Finally, multivariate meta regression on post-partum relapse rate was performed including all variables of interest (mid-year of data collection, diagnostic criteria, data source, proportion exposed to DMT post-partum, and proportion breast-feeding) in order to establish the impact on heterogeneity when including all potential modifiers in the model.

Statistical significance was set at p<0.05 in all analyses. All analyses were performed in stata v16.1 (Statacorp).

**Data availability**

This work used published data and existing Stata scripts. Data sources are presented in the PRISMA statement (supplementary data).

**Results**

*Search results*

1066 individual records were identified (1063 through publication databases, an additional 3 through other sources). Of these, 811 were excluded through review of title and article descriptors. 255 abstracts were assessed for eligibility and 150 full text articles retrieved for review. The majority of studies excluded at this stage were studies examining the effect of disease modifying therapy (DMT) on fetal outcomes, with no data given on maternal relapse rates. Other notable exclusions were 8 clinical trials of IVIg (6 studies) or IV methylprednisolone (2 studies) either during pregnancy or post-partum to prevent relapses, 1 clinical trial of vitamin D during pregnancy, and 4 studies consisting of subgroups of patients included in subsequent publications (supplementary data 1).

Data from 27 papers and 1 conference presentation were included in the final synthesis. Details of included studies are given in table 1 and full references in supplementary data 2.

*Population demographics*

A total of 7034 MS pregnancies in 6430 women were included in this meta-analysis. Data were available from a total of 28 studies, which were split into 34 cohorts for the purposes of analysis (table 1). Where provided, the range of mean age at pregnancy was 28.4-34.8 (median of mean age 31; IQR 30.2-31.9). Range of mean disease duration at the time of pregnancy was 2.8-10.7 years and range of median EDSS 0.7-2.4 (table 1). 7 studies did not state the MS subtype of included participants; of the remaining studies 15/21 included only patients with relapsing remitting MS. Of the remaining 6 studies, 3 included <5% individuals with progressive disease and all had <20% individuals with progressive disease.

*Overall relapse rates and change over time*

Meta-analysis of all studies with available data demonstrated a decrease in ARR during pregnancy, followed by post-partum rebound (figure 1a). Overall ARR by trimester of pregnancy, and broken down by mid-year of data collection are given in table 2.

There was a significant difference between relapse rates between mid-year of data collection groups pre-pregnancy (p<0.01), during the first (p=0.03) and second (p=0.02) trimesters, and post-partum (p<0.01) (table 2 and figure 1b, forest plots given in supplementary data 2). Meta regression by mid-year of data collection was then performed. No statistically significant relationship was seen between mid-year of data collection and ARR pre-pregnancy or during the third trimester (data not shown), however over time there was a significant decrease in relapse rates in the first trimester (co-efficient 0.021, p=0.033, not shown), second trimester (co-efficient 0.021, p=0.016, not shown) and post-partum (co-efficient 0.06, p<0.001) (table 2 and figure 2).

Heterogeneity was high (I2 96.7-98.5% depending on trimester) for both the overall meta-analysis; neither subgroup analysis according to mid-year of data collection nor regression by mid-year of data collection substantially changed this (table 2). Subgroups were 1994-2004 (pre-widespread DMT use), 2005-2009 (first line injectable DMT use dominant) and 2010-present (increasing use of highly effective therapies).

Taking account of diagnostic criteria used in individual studies (19 cohorts from 17 studies) using subgroup analysis and meta-regression did not substantially reduce heterogeneity of relapse rate either prior to pregnancy, during any trimester, or post-partum (data not shown).

Assessment of bias using funnel plots and Egger p value did not reveal any significant bias for either the pooled or subgroup analyses. Analysis exploring the potential effect of the total time for cohort collection did not reveal any significant effect on ARR at any stage of pregnancy, and did not impact on between-study heterogeneity.

*Effect of disease modifying treatment (DMT)*

A pre-specified potential cause of change over time and between-study heterogeneity was the change in practice around DMT use over time. When meta regression was used to explore the possible relationship between the proportion of the population using DMT at any point in the 2 years prior to pregnancy and ARR at any time during pregnancy (29 studies included; range 0-100% using DMT; median 59%, 6229 individuals), no significant relationship was seen (data not shown). Similarly, the proportion of the population reported to be taking DMT at the time of conception (i.e. exposed pregnancies; 24 studies with range 0-100% using DMT; median 25%, 5442 individuals) was not associated with ARR either prior to or during pregnancy, or post-partum (data not shown). Where breakdown was given by DMT, this was generally reported at the population level outside of studies examining specific DMTs (e.g. Natalizumab). In general, the only DMTs continued to conception were first line injectable (the majority of patients) or Natalizumab (small numbers outside of focused studies, see table 1).

Finally, the proportion of the population restarting DMT within 3 months post-partum (21 studies with range 0-89% restarting DMT; median 18%, 5483 individuals) was not significantly associated with ARR in the 3 months post-partum period (p=0.27, figure 3a). Only 5 studies reported the proportion restarting highly active DMT, of which 2 reported no patients restarting such medication (range 0-76%). Due to the majority of studies not providing breakdown by DMT type, and the heterogeneity between the three studies where highly active DMT was restarted, it was judged to be invalid to study association(s) with different DMTs.

*Effect of breastfeeding on post-partum relapse rate*

It has been postulated that increasing rates of breastfeeding are responsible for a reduction in post-partum ARR (15). In order to assess this, meta regression was performed using reported rates of breastfeeding where available (17 cohorts from 13 studies; range 0-100% population reporting breast feeding; median 54%). There was no significant relationship between the proportion of the population breastfeeding and post-partum ARR (meta regression p=0.088), and the proportion of the population breastfeeding did not explain the heterogeneity in post-partum relapse rates (residual I2 92.51) (figure 3b). Exclusive breastfeeding was only reported in a minority of studies, all of which had set out to examine this specifically (table 2), in all other studies reporting breastfeeding rates it was variable and/or unclear as to the definition of breastfeeding used.

*Data source and method of data collection*

Firstly, in order to examine whether the data source (claims database vs MS database vs pregnancy focused database) influenced the results we divided studies into subgroups on this basis. Those studies using data originating from claims databases demonstrated a lower relapse rate at all time points, driving a significant difference between the groups during the first two trimesters of pregnancy and the post-partum period (figure 4). Heterogeneity was high in all three subgroups in the pre-pregnancy period, but reduced both during pregnancy and in the post-partum period between studies taken from claims databases (I2=33% T1, 12% T2, 0.1% T3 and 0.04% T4). Heterogeneity remained high in both the MS database, and pregnancy-focused database subgroups. When the two studies using claims databases as the primary data source were excluded from analyses, high heterogeneity remained throughout.

The association between mid-year of data collection and annualized relapse rate remained significant for both relapse rate pre-pregnancy (p=0.017) and postpartum (p=0.006) (data not shown).

Finally, subgroup analysis was performed according to whether the data during pregnancy were collected prospectively or retrospectively. No relationship was seen between methods of data collection and ARR at any stage during pregnancy.

*Inclusion of all variables*

When all variables were included in a random effects multivariate meta regression (8 cohorts from 6 studies), the overall model was non-significant. Heterogeneity remained high (residual I2 96.3%) indicating that the model did not explain the underlying variation between studies (data not shown).

**Conclusions**

Despite high heterogeneity between individual studies, this meta-analysis demonstrates that the historic assumption that ARR reduces during pregnancy and increases again post-partum remains true, despite significant changes in the MS treatment landscape, and increasing rates of treatment with DMT. Conversely, MS ARR appears to be decreasing over time in women both prior to pregnancy and in the post-partum period. The only single significant contributor to this change over time appeared to be the data source used. Claims databases, which are relatively over-represented in more modern cohorts and very heavily weight the analysis due to the number of individuals, had a significantly lower relapse rate both during the first two trimesters of pregnancy and in the post-partum period. Neither diagnostic criteria, DMT exposure, nor proportion of women breastfeeding appears to associate with the change in relapse rate at a population level. Similarly, including all potential variables in a multivariate meta regression did not significantly impact on overall heterogeneity.

Whilst there was little heterogeneity between the data taken from claims databases, this must be interpreted in the context of the estimates from these data sources. The estimated ARR at all time points from the claims databases is lower than from other data sources; significantly so during early pregnancy and in the post-partum period. The reason(s) for this discrepancy remain unclear from this study, but may include the inclusion of milder MS cases in these data sources (as opposed to MS or pregnancy-focused data sources predominantly including those potentially eligible for DMT or seen in referral centers), or alternatively the under-reporting or recording of MS relapses in these databases. Additionally (or alternatively), there may be a relative over-representation of those with progressive disease in these cohorts (as neither specified MS type); however given the relatively young mean age in each of these studies it seems unlikely that this would have had a major impact on the overall relapse rate. Pregnancy registry studies report a higher pre-pregnancy ARR compared to MS database studies. The reason(s) for this are unclear, but may represent under-reporting of MS relapses to physicians prior to pregnancy, but more vigilant reporting during pregnancy in all individuals.

It could be argued that the high heterogeneity observed in our work limits the interpretation of the results. Given that the only subgroup analysis that appeared to overcome this was when categorising studies by data source, it seems likely that features related to clinical and/or data collection methodology are driving this to at least some degree. However, we would argue that this heterogeneity reflects what is seen in clinical practice. Interestingly, those studies using MS databases with post hoc selection of pregnant patients gave very similar relapse rates in early pregnancy, despite the potential for recall bias - patients recruited to pregnancy-specific studies may often only provide truly prospective information from the end of the first trimester, whereas those in MS databases should have data recorded in a similar manner throughout. Despite this heterogeneity, the signal for decreasing relapse rate over time remains strong through all subgroup analysis and cannot be ignored.

When using the results of this meta-analysis to inform clinical practice, the limitations of this study must be considered. Effects seen at a population level do not always translate directly to advice that can be given to individual patients; such discussions need to take account of individual risk-benefit analyses. Unfortunately, due to small numbers, it was not possible to look at the subgroup of women continuing highly active DMT until conception in this analysis. First line DMT do not generally reach their peak effects until up to 12 weeks of therapy, and it is likely that any effect of early resumption of highly active DMT on post-partum rebound in ARR is masked in this population-level analysis, due to a large effect size on only a small proportion of the population. The majority of studies reporting DMT resumption did not provide a breakdown by DMT type (highly active vs platform therapies); further studies are required to examine the effect of DMT type on post-partum relapse rate.

Using the mid year of data collection to stratify studies does not fully capture the variation in recruitment between studies, as it does not take account of the length of recruitment. Whilst we tried to overcome this limitation to a certain degree by using a secondary analysis based on MS diagnostic criteria, this remains a potentially significant source of heterogenetity.

Using overall reported rates of breastfeeding to examine the effect of breastfeeding on post-partum relapse rate is a relatively crude measure. Recent work has tried to examine this in more detail than in our study, however this recent meta-analysis did not study change in relapse rate over time [15]. Hormonal effects of breastfeeding leading to suppression of ovulation appear to only persist with (almost) exclusive breastfeeding, consisting of 3-4 hourly breastfeeding during the day and at least one feed overnight [[10]](https://paperpile.com/c/WIATem/nWQS). Breastfeeding rates often do not take account of combination feeding, which can impact on hormonal changes in the mother. In addition, these analyses do not consider selection bias - women with more active disease pre-pregnancy may be less likely to choose to breastfeed, and more likely to resume DMT at an earlier stage [[11]](https://paperpile.com/c/WIATem/KnwX). Despite these limitations, it seems unlikely from this meta-analysis that breastfeeding is the sole driver of the dramatic, more recent, decline in post-partum relapse rates, whereas in the US breastfeeding rates have been slowly and gradually increasing [[12]](https://paperpile.com/c/WIATem/SIlR), and this slow rate of change is likely to be similar globally.

In conclusion, given that that the overall prevalence of MS is increasing [[13]](https://paperpile.com/c/WIATem/LDAd0), and evolving diagnostic criteria have led to people being diagnosed earlier [[14]](https://paperpile.com/c/WIATem/me9Cb), an increasing number of women with MS are facing complex questions about DMT and family planning. This meta-analysis suggests that ARR is lower both prior to pregnancy and postpartum, and this is unlikely to be due to any single factor. Whilst our analysis did not show a relationship between pre-pregnancy relapse rate and DMT exposure, it would seem likely that a combination of advising women with MS at high risk of relapse regarding continuing DMT until conception, together with diagnostic shift increasing the number of women with less active MS could be driving these changes. Similarly, the attenuation that is seen in post-partum rebound of relapse rate may be due to early resumption of DMT in those with active disease, alongside increased rates of breastfeeding in those with less active disease, however, the limitations of population-level meta-analysis do not allow this granularity of analysis.

**Figures**

**Figure 1:** MS relapse rate by trimester of pregnancy

1. Overall annualised relapse rate by trimester
2. Annualised relapse rate by trimester according to mid year of data collection

**Figure 2:** Meta regression bubble plot demonstrating significant change in post partum ARR over time

**Figure 3:** Meta regression bubble plots demonstrating:

1. No association between the proportion of women restarting DMT and ARR post-partum
2. No association between the proportion of women breastfeeding and ARR post-partum

**Figure 4:** Annualised relapse rate by trimester according to data source

**Supplementary data**

**Supplementary data 1:** PRISMA flow diagram

**Supplementary data 2:** studies used in meta-analysis

**Supplementary figure 1:** Forest plots of overall annualised relapse rates, split by mid year of data collection

1. Prior to pregnancy
2. Trimester 1
3. Trimester 2
4. Trimester 3
5. 3 months post-partum (Trimester 4)

**Appendix: Author contributions**

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| --- | --- | --- |
| **Name** | **Location** | **Contribution** |
| Dr Ruth Dobson | Queen Mary University London | Conceived the idea of the study, performed initial literature search, performed statistical analysis, drafted initial manuscript |
| Dr Vilija Jokubaitis | Monash University, Melbourne | Conceived the idea of the study, performed secondary literature search and reviewed selected manuscripts, input into statistical analysis, substantially contributed to manuscript |
| Prof. Gavin Giovannoni | Queen Mary University London | Conceived the idea of the study, input into statistical analysis, substantially contributed to manuscript  |

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