# Postpartum Relapse Rates in Women with Relapsing Multiple Sclerosis and the Impact of Disease-Modifying Therapy: A Systematic Review

**K. Hellwig, E. Verdun di Cantogno, M. Sabidó**

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## CONCLUSIONS

**Findings regarding postpartum relapses in women with MS exposed to DMT show a complex and often conflicting picture.**

**Limited evidence suggests high-efficacy DMT preconception (with no exposure during pregnancy) increases risk of postpartum relapse, likely due to higher disease activity in these patients.**

**Decision-making concerning benefit-risk of DMT use before (preconception), during, and after pregnancy for treating MS remains challenging.**

**DMT**, disease-modifying therapy; **MS**, multiple sclerosis.

## INTRODUCTION

- MS is the most common neurologic disability in women of child-bearing age, with average peak onset of disease at 30 years of age.[1]
- Pregnancy is widely accepted as a period in which MS relapses are decreased; however, studies generally show an increased risk of relapse immediately postpartum.[2,3]

**DMT**, disease-modifying therapy; **MS**, multiple sclerosis.

## OBJECTIVES

**To evaluate postpartum relapses according to treatment decisions before (preconception), during, and after pregnancy in women with MS treated with DMTs, including the influence of treatment with DMTs and timing of DMT restart.**

## METHODS

- Searches of MEDLINE and EMBASE databases were conducted to identify relevant articles from November 2009–2019.
  - RCT or observational studies were considered but not systematic reviews, case series, or case reports.
  - Conference abstracts from 2015 onwards were also included.

### Search Terms

- MS
- Pregnancy
- DMT*
- Relapse, recurrence, or flare up (as outcome)

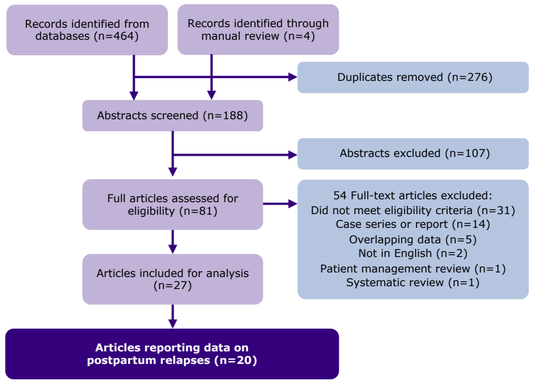
### Article Inclusion Criteria

- Focus on patients with MS treated with DMTs
- Timing of DMT exposure identified
- Timing of relapses identified
- Reported comparison† expressed by HR, RR, OR, or mean relapses

*Interferon beta-1a, interferon beta-1b, peginterferon beta-1a, alemtuzumab, cladribine, dimethyl fumarate, fingolimod, glatiramer acetate, laquinimod, natalizumab, teriflunomide, methotrexate, cyclophosphamide, mycophenolate mofetil, azathioprine, and rituximab. †Comparisons were established in women with MS treated with DMTs who discontinued treatment vs those who did not discontinue according to timing of discontinuation (before or during pregnancy) and, according to timing of restarting of DMT among those who had discontinued DMT. **DMT**, disease-modifying therapy; **HR**, hazard ratio; **MS**, multiple sclerosis; **OR**, odds ratio; **RCT**, randomized control trial; **RR**, relative risk.

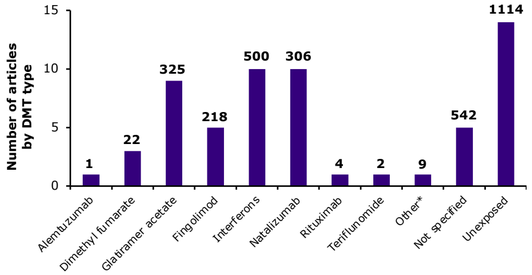
## RESULTS

### Figure 1. Flow of identification, screening, eligibility, and inclusion




- Across 20 studies[4–23], **3185 patients** and **3520 pregnancies** that provide data on postpartum relapses were included.
- **1927** pregnancies were exposed to DMT **preconception**, **598 during pregnancy**, and **704** in the **postpartum period**.

### Figure 2. DMT that patients were exposed to before (preconception), during, and after pregnancy




Figures displayed above the bars denote the number of patients receiving a particular DMT.
*Monthly intravenous immunoglobulin.

**CI**, confidence interval; **DMT**, disease-modifying therapy; **HR**, hazard ratio; **OR**, odds ratio.

### DMT exposure (preconception vs unexposed)

- Five studies found use of DMT preconception did not have an effect on the risk of postpartum relapses for ≤1 year vs those not treated with DMT.[4–8]
  - Where specified, most patients were treated with injectable DMT (e.g., interferon beta and glatiramer acetate).[7,8]

### Type of DMT exposure (high-efficacy vs moderate-efficacy)

- Three studies reported higher rates of relapses with high-efficacy DMT (e.g., natalizumab and fingolimod) preconception compared to moderate-efficacy DMT or no DMT.[9–11]
  - One study found preconception use of high-efficacy DMT was associated with higher postpartum relapses (OR 2.11 [95% CI: 1.32–3.27]) vs those not treated.[9]
- A study of natalizumab-treated patients noted earlier discontinuation prior to conception was associated with a larger increase in the risk of relapse after delivery ($p<0.021$).[10]

### Figure 3. DMT exposure (during pregnancy vs unexposed)

Seven studies evaluated the effect of DMT exposure during pregnancy on postpartum relapses[6,12–17]

Four studies reported patients exposed to DMT during pregnancy, generally within the first trimester, had fewer postpartum relapses vs those without DMT exposure[13–16]

Noted in both women treated with moderate-[14,15] and high-efficacy DMTs[13,16]

Three studies reported no relevant differences in the risk of postpartum relapses between patients who were and were not exposed to DMT during pregnancy[6,12,17]

### Figure 4. Timing of DMT restart (postpartum)

Nine studies evaluated the effect of timing of DMT restart on postpartum relapses[4,8,9,10,18–22]

Six studies suggest that restarting DMT early (1 week to 1 year) after delivery may reduce risk of relapses in the postpartum period[4,9,10,18–20]

E.g., a cohort study found restarting DMT within 1 year postpartum and shorter duration to restart significantly reduced the risk of relapses (OR 0.59 [95% CI: 0.25–0.88] and 0.92 [95% CI: 0.88–0.93] per week from delivery, respectively)[9]

Three studies reported no association between relapse risk and timing of DMT restart after birth[8,21,22]

E.g., one study found restarting interferon beta or glatiramer acetate within 2 weeks of delivery did not reduce risk of relapse over 2 years postpartum (HR 1.3 [95% CI: 0.5–3.4])[22]

1. Baird SM, Dalton J. *J Perinat Neonatal Nurs*. 2013;27:232–241. 2. Confavreux C, et al. *N Eng J Med*. 1998;339:285–291. 3. Vukusic S, et al. *Brain*. 2004;127:1353–1360. 4. Portaccio E, et al. *J Neurol Neurosurg Psychiatry*. 2014;85:845–850. 5. Portaccio E, et al. *Neurology*. 2011;77:145–150. 6. Pardo K, et al. *Mult Scler*. 2018;24:509–510. 7. Hellwig K, et al. *JAMA Neurol*. 2015;72:1132–1138. 8. Jesus-Ribeiro J, et al. *Mult Scler Relat Disord*. 2017;17:63–68. 9. Bsteh G, et al. *Mult Scler*. 2020;26:69–78. 10. Portaccio E, et al. *Neurology*. 2018;90:e832–e839. 11. Manieri MC, et al. *Mult Scler*. 2018;24:352. 12. Cuello JP, et al. *Med Clin (Barc)*. 2020;154:214–217. 13. Alroughani R, et al. *Neurology*. 2019;92:P4.2093. 14. Fragoso YD, et al. *Clin Neurol Neurosurg*. 2013;115:154–159. 15. Hellwig K, et al. *Ther Adv Neurol Disord*. 2012;5:247–253. 16. Hellwig K, et al. *Mult Scler*. 2011;17:958–963. 17. Herbstritt S, et al. *Mult Scler*. 2015;23:112–113. 18. Hemat S, et al. *Mult Scler*. 2018;24:74–75. 19. Popova E, Boyko A. *J Neurol Sci*. 2015;357:e300. 20. Vukusic S, et al. *Mult Scler*. 2015;21:953–955. 21. Langer-Gould A, et al. *Neurology*. 2020;94:e1939–e1949. 22. Beaber BE, et al. *Perm J*. 2014;18:9–13. 23. Alroughani R, et al. *Neurology*. 2018;90:1–7.

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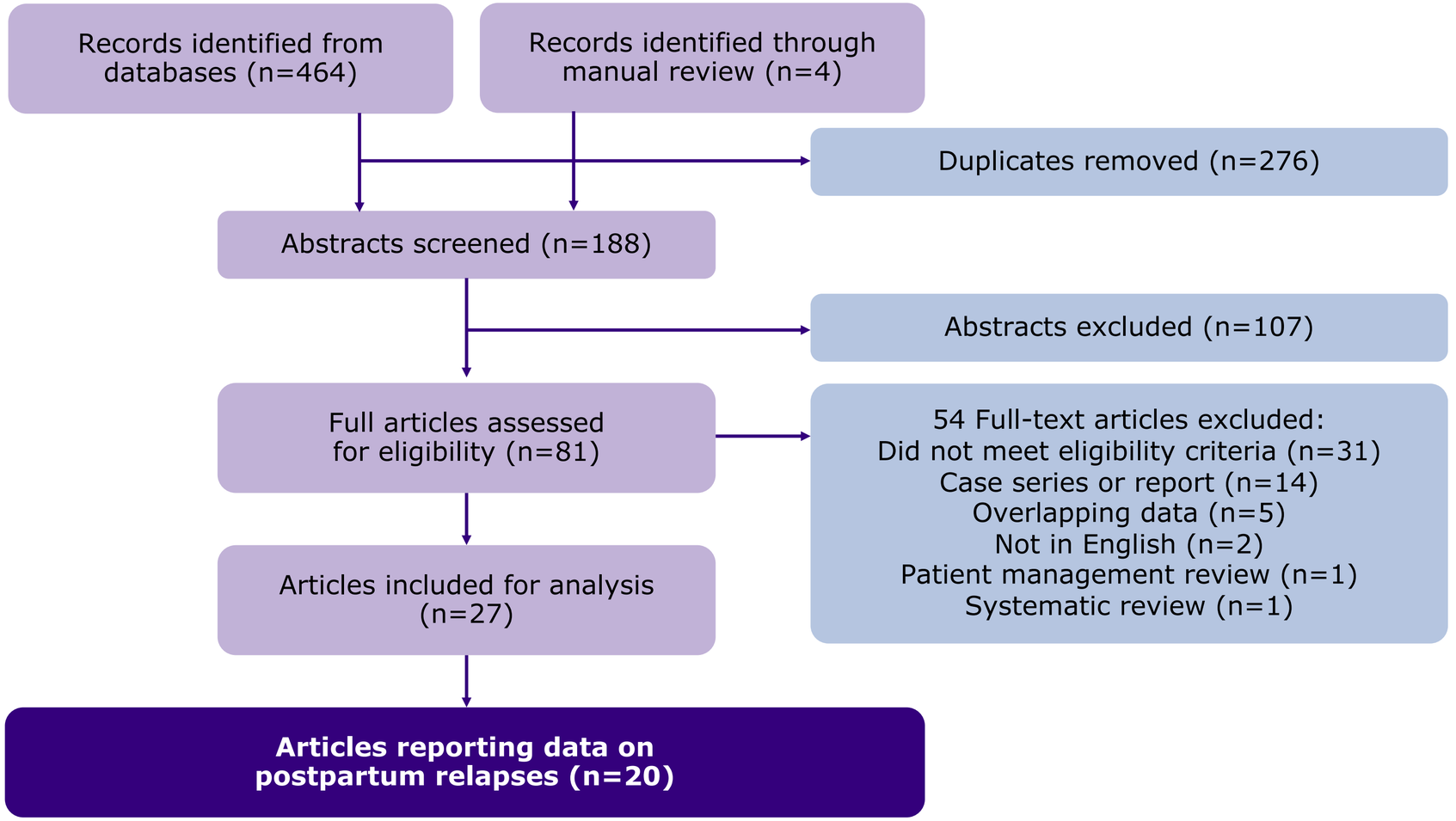

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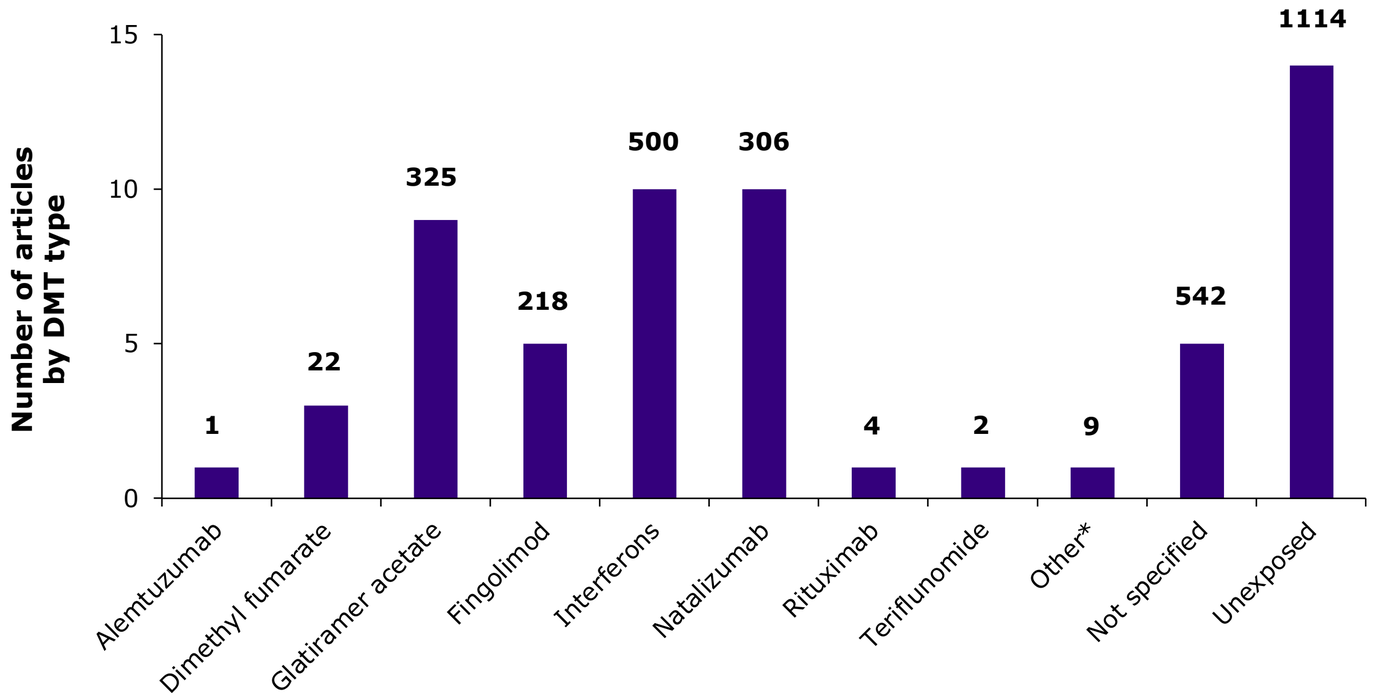


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