Postpartum Relapse Rates in Women With Relapsing Multiple Sclerosis and the Impact of Disease-Modifying Drugs: A Systematic Review

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Disclosures

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- **EDVC** is an employee of Ares Trading S.A., Eysins, Switzerland, an affiliate of Merck KGaA, Darmstadt, Germany
- **MS** is an employee of Merck KGaA, Darmstadt, Germany
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Introduction

- MS is the most common neurologic disability in women of child-bearing age, with an 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]

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 other factors

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

1. Baird SM and 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.

Methods

- Searches of Medline and EMBASE databases were conducted to identify relevant articles from November 2009–2019
  - RCTs 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
- DMTs*
- Relapse, recurrence, or flare up (as outcome)

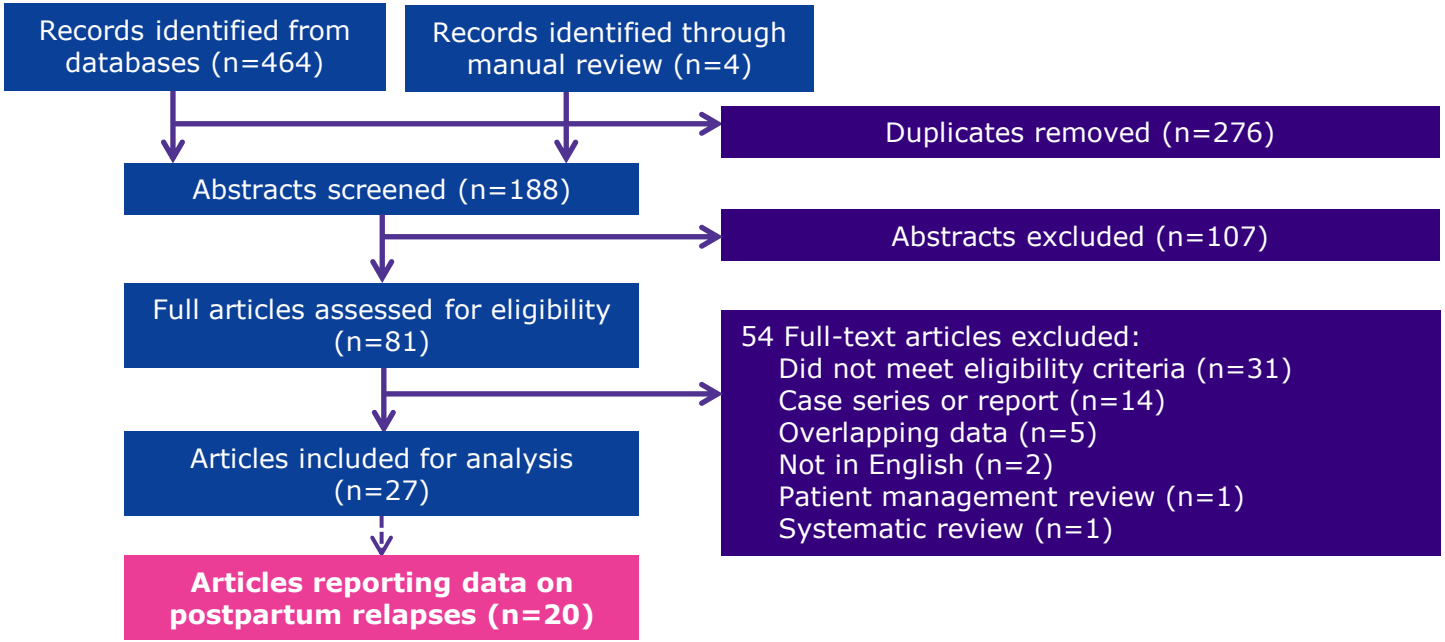
ARTICLE INCLUSION CRITERIA

- 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 tablets, dimethyl fumarate, fingolimod, glatiramer acetate, laquinimod, natalizumab, teriflunomide, methotrexate, cyclophosphamide, mycophenolate mofetil, azathioprine, ocrelizumab, 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 treatment among those who had discontinued DMTs.
DMT, disease-modifying therapy; **HR**, hazard ratio; **MS**, multiple sclerosis; **OR**, odds ratio; **RCT**, randomized control trial; **RR**, relative risk.

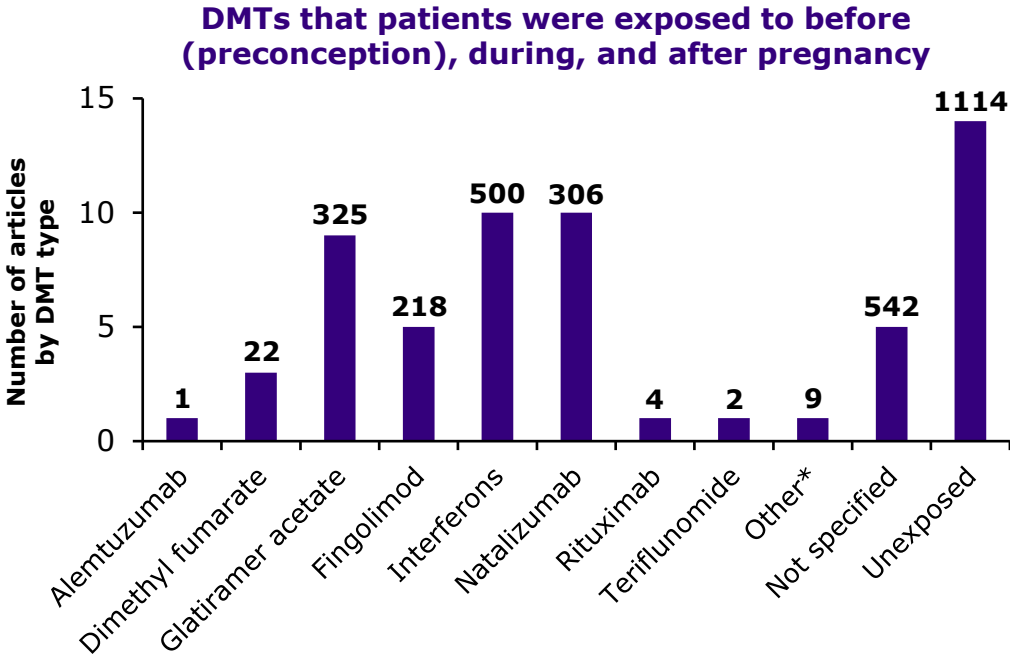
Results

Flow of identification, screening, eligibility, and inclusion



Results

- Across 20 studies, **3185 patients** and **3520 pregnancies** that provided data on postpartum relapses were included
- **1927** pregnancies were exposed to DMTs **preconception**, **598 during pregnancy**, and **704** in the **postpartum** period



Figures displayed above the bars denote the number of patients receiving a particular DMT.

*Monthly intravenous immunoglobulin.
DMT, disease-modifying therapy

Results

DMT exposure (preconception vs unexposed)

- Five studies found that use of DMTs preconception did not have an effect on the risk of postpartum relapses for ≤1 year vs those not treated with DMTs[1–5]
  - Where specified, most patients were treated with injectable DMTs (e.g., interferon beta and glatiramer acetate)[4,5]

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

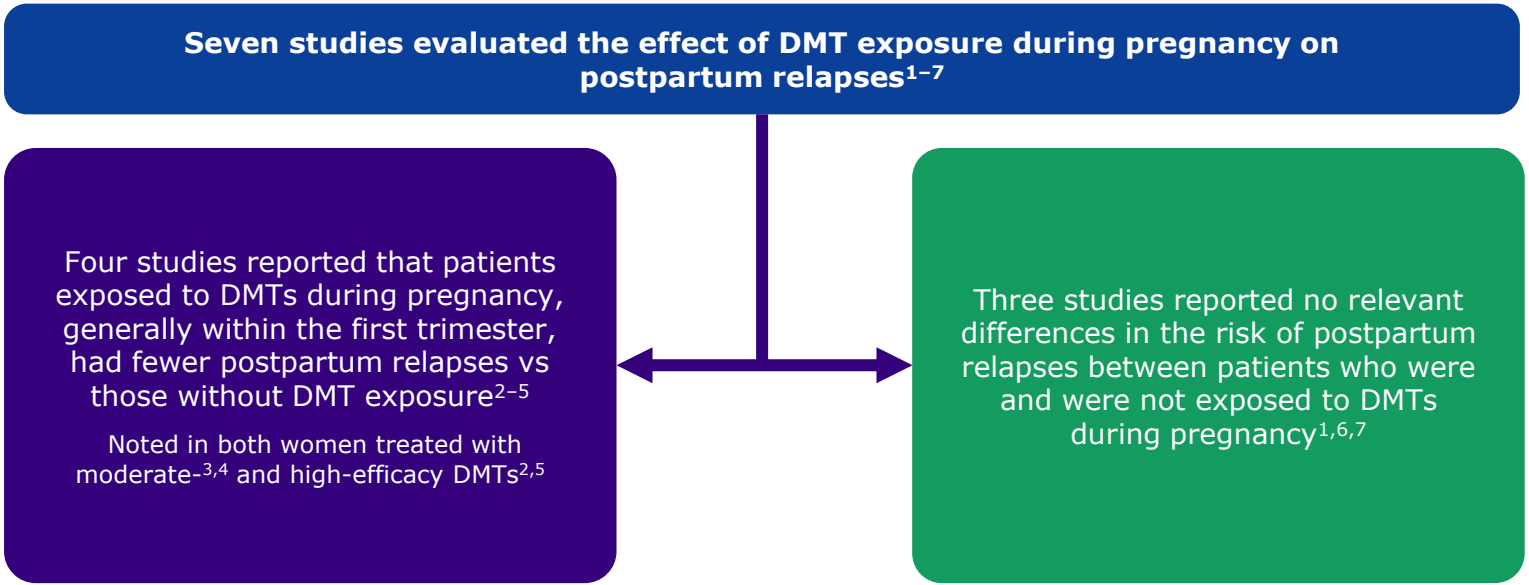
- Three studies reported higher rates of relapses with the preconception use of high-efficacy DMTs (e.g., natalizumab and fingolimod) compared to moderate-efficacy DMTs or no DMTs[6–8]
  - One study found that use of high-efficacy DMTs preconception was associated with higher postpartum relapses (OR 2.11 [95% CI: 1.32–3.27]) vs no DMTs[6]
- 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 ($p<0.021$)[7]

DMT, disease-modifying therapy; **OR**, odds ratio.

1. Portaccio E, et al. *J Neurol Neurosurg Psychiatry*. 2014;85:845–850. 2. Portaccio E, et al. *Neurology*. 2011;77:145–150. 3. Pardo K, et al. *Mult Scler*. 2018;24:509–510. 4. Hellwig K, et al. *JAMA Neurol*. 2015;72:1132–1138. 5. Jesus-Ribeiro J, et al. *Mult Scler Relat Disord*. 2017;17:63–68. 6. Bsteh G, et al. *Mult Scler*. 2020;26:69–78. 7. Portaccio E, et al. *Neurology*. 2018;90:e832–e839. 8. Manieri MC, et al. *Mult Scler*. 2018;24:352.

Results

DMT exposure (during pregnancy vs unexposed)



DMT, disease-modifying therapy.

1. Cuello JP, et al. *Med Clin (Barc)*. 2020;154:214–217. 2. Alroughani R, et al. *Neurology*. 2019;92:P4.2093. 3. Fragoso YD, et al. *Clin Neurol Neurosurg*. 2013;115:154–159. 4. Hellwig K, et al. *Ther Adv Neurol Disord*. 2012;5:247–253. 5. Hellwig K, et al. *Mult Scler*. 2011;17:958–963. 6. Herbstritt S, et al. *Mult Scler*. 2015;23:112–113. 7. Pardo K, et al. *Mult Scler*. 2018;24:509–510.

Results

Timing of DMT restart (postpartum)

Nine studies evaluated the effect of timing of DMT restart on postpartum relapses[1–9]

Six studies suggest that restarting DMT early (1 week to 1 year) after delivery may reduce risk of relapses in the postpartum period[1–6]

E.g., a cohort study found that 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)[6]

Three studies reported no association between relapse risk and timing of DMT restart after delivery[7–9]

E.g., one study found that 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])[9]

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

1. Portaccio E, et al. *Neurology*. 2018;90:e832–e839. 2. Portaccio E, et al. *J Neurol Neurosurg Psychiatry*. 2014;85:845–850. 3. Hemat S, et al. *Mult Scler.* 2018;24:74–75. 4. Popova E and Boyko A. *J Neurol Sci*. 2015;357:e300. 5. Vukusic S, et al. *Mult Scler.*;2015;21:953–955. 6. Bsteh G, et al. *Mult Scler.* 2020;26:69–78. 7. Langer-Gould A, et al. *Neurology.* 2020;94:e1939–e1949. 8. Jesus-Ribeiro J, et al. *Mult Scler Relat Disord*. 2017;17:63–68. 9. Beaber BE, et al. *Perm J*. 2014;18:9–1315.

Conclusions

- Findings regarding postpartum relapses in women with MS exposed to DMTs show a complex and often conflicting picture
- Limited evidence suggests that use of high-efficacy DMTs 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

FULL MANUSCRIPT ACCEPTED FOR PUBLICATION

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