Pregnancy and MS

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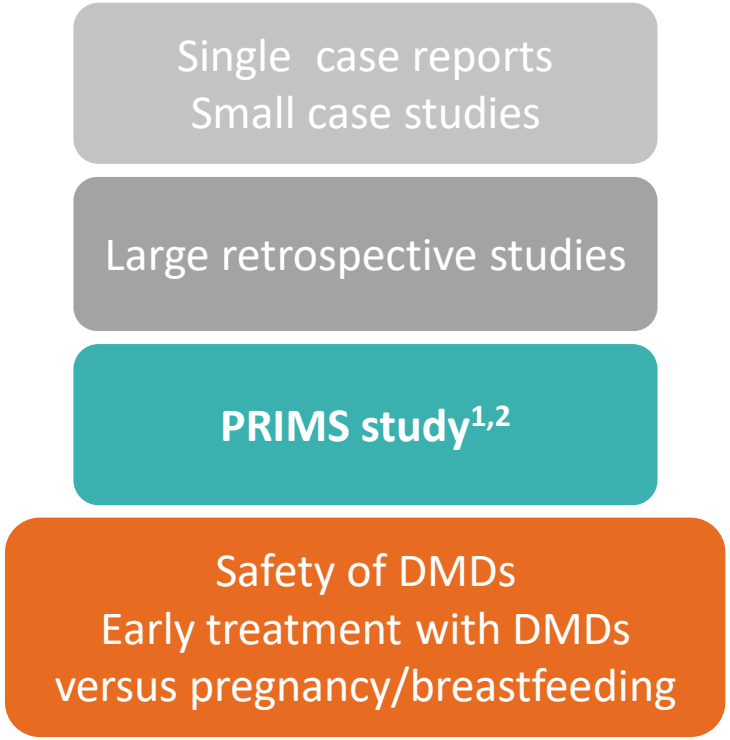
Paradigm evolution

- 1950–1960: Women with MS were advised to avoid pregnancy
- 1970–90: Women with MS were informed about the risks of pregnancy
- 1998: ‘change of paradigm’
- After 2000: women were offered early treatment with DMDs



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FAMILY PLANNING

- Women with MS should receive support and counseling on issues of posible pregnancy
- Decision to start or expand a family is complicated for MS patients
- Some pregnancies are unplanned (% depend on the country)
- Optimal conception timing to minimize time off therapy is very important
- Disease control before, during and after pregnancy is needed (Example: our pregnancy consultation on mondays)

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Coyle, P, 2014, D´hooghe MB, 2012.

Family planning issues in MS

Fertility	Pre-pregnancy	Pregnancy	Postpartum
• Contraception choice • Fertility and fetal development • DMT use and recommended washout periods • Assisted reproductive technology/*in vitro* fertilization	• Impact on the female vs male patient • Basic counseling • Genetic risk • Pregnancy impact on MS prognosis (early and late) • Impact of MS on ability to care for children • Economic and social burden of having children	• Disease activity • DMT use • Evaluation and treatment of relapses and disease symptoms • Delivery and anesthesia choice	• Disease activity • Breastfeeding • DMT use • Impact on infant/child development

DMT, disease-modifying therapy.

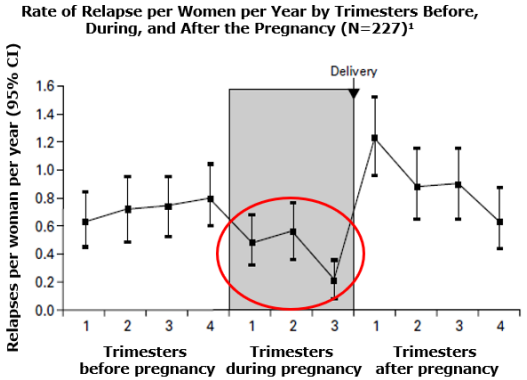
1. Coyle P. Ther Adv Neurol Disord 2016;3:198–210.

Impact of pregnancy on relapses

- Rate of pregnancy-related relapse in MS[1]
  - 227 pregnancies resulting in a live birth
  - Relapse rate per woman per year for each 3-month period before, during, and after pregnancy. Year before pregnancy: 0.7±0.9; first trimester: 0.5±1.3 (p=0.03 vs. rate before pregnancy); second trimester: 0.6±1.6 (p=0.17); third trimester: 0.2±1.0 (p<0.001); first three months postpartum 1.2±2.0 (30%) (p<0.001). (Confavreux et al. New Engl J Med 1998)

- MS Base: 14% relapses in postpartum (889 pregnancies) (2014)

- Predictors of relapses in the postpartum period[2]
  - Greater relapse rate in the year preceding the pregnancy or during the pregnancy
  - Higher EDSS score at pregnancy onset



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1. Confavreux et al. New Engl J Med 1998; 2. Vukusic et al. Brain 2004

ASSISTED REPRODUCTIVE TECHNIQUES IN MS

- More pregnancies with GnRH agonists (40%) than with antagonists (10%)
- Controversy : Agonists or antagonist ? increase of relapses?
- Two French studies and one Argentinian study : Agonists increase relapse risk and radiological disease activity
- German study: Relapse rate increases during the first three months after ART independent from gonadotropin use
- It seems that treatment with GnRN antagonists is not related with an increase in relapses

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Michel 2012 , Hellwig K 2009, Correale 2012
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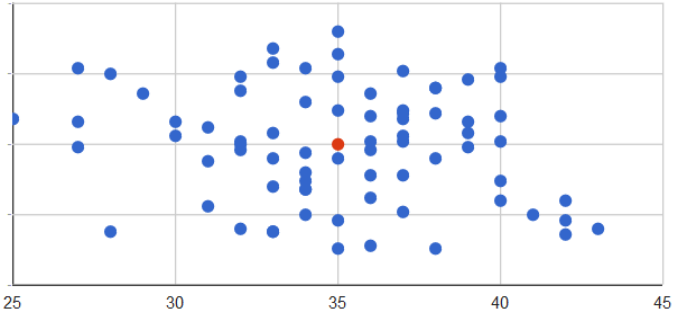
Impact of MS on pregnancy and fetal outcome

- MS is not generally associated with negative effects on pregnancy and fetal outcome:[1–4]
  - lower mean birth weight, preterm birth[1,4]
  - increased frequency of birth-induced and surgical procedures[1,4]
  - mainly in women with high level of disability[3]
- MS is not related to a condition of ‘high risk’ pregnancy

1. Dahl et al. Neurology 2005; 2. Sadovnick et al. Arch Neurol 1994;
3. van der Kop et al. Ann Neurol 2011; 4. Jalkanen et al. Mult Scler 2010

Pregnancy and obstetrical outcomes in our cohort of women with RRMS

- 76 pregnancies were prospectively followed in the last 4 years (Cohort of 1166 patients) :



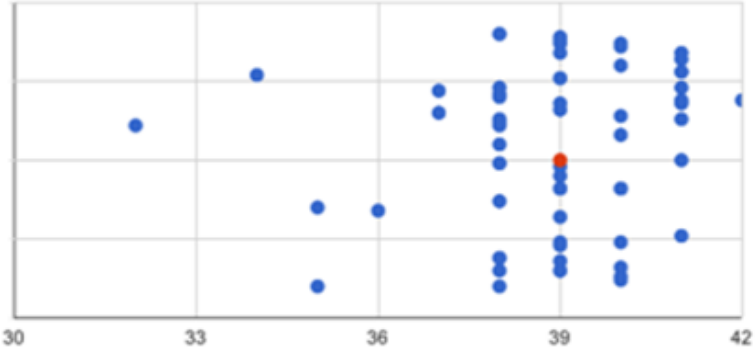
Age of pregnant women

- Mean age was 35 (25-43)
- mean BMI 20
- mean disease duration 75 months.
- 17% received ART.
- 20% of patients have had an spontaneous abortion in the first trimester
- 9% gestational diabetes.

Pregnancy and obstetrical outcomes in our cohort of women with RRMS

- Mean duration of pregnancy was 39 ± 1,7 weeks
- C-sections were performed in 23% of them
- 18% of patients didn´t receive anesthesia during the vaginal birth
- All pregnancies resulted in live births, with no complications

- Mean weight of newborns:3120 gr
- Mean height of newborn 49,70 cm
- 2% of malformations in newborns

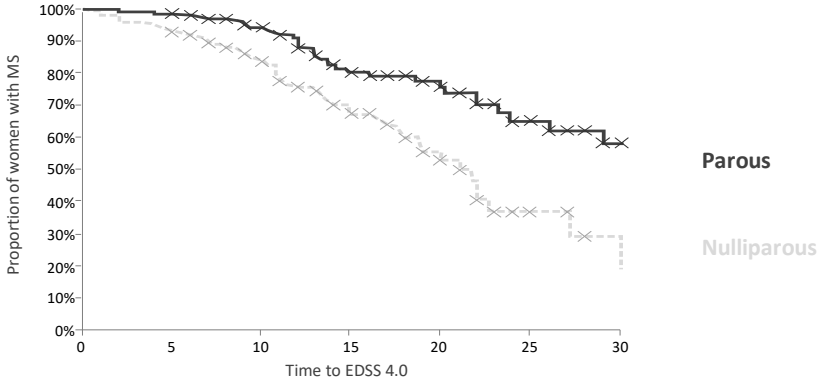


Duration of pregnancy (weeks)

The impact of pregnancy on long-term disability progression

- A retrospective study assessed data from 445 female MS patients (261 nulliparous, 184 'parous' after MS onset) to investigate the long-term effect of pregnancy on disability[1]
- 'Parous' women took significantly longer to reach:[1]
  - EDSS score 4 vs. nulliparous women (13 years vs. 9 years; p <0.001)
  - EDSS score 6 vs. nulliparous women (15 vs. 12 years; p = 0.02)

Time to reach EDSS score 4 in nulliparous and 'parous' women with MS



Pregnancy is major modifier of disease activity in MS

Jokubaitis VG. Ann Neurol 2016

In 2,466 patients followed up for at least 10 years, there was evidence of long-term protective effects of pregnancy against disability accrual.

1. Masera S *et al. Mult Scler.* 2015;21(10): 1291-1297.

Change in Pregnancy categories (FDA)

- The FDA recently issued a new rule that will apply to pregnancy language in product package inserts (PI)1
- The new guidance provides a framework for clearly communicating information on the benefits and risks of using a drug during pregnancy and lactation to help facilitate prescribing decisions2
- As of June 30, 2015, new products will not be assigned pregnancy categories (A, B, C, D, X) 1
- For existing products, a label change with revised language will require FDA review and approval1
- Labels will still include known pregnancy, fertility, and lactation data in both animal and human studies and experience1

Subsections	Example of Subheadings
Pregnancy	• Disease associated maternal and/or embryo/fetal risk • Dose adjustments during pregnancy and the postpartum period • Maternal adverse reactions • Fetal/neonatal adverse reactions • Labor or delivery • Human data • Animal data
Lactation	• Must clearly describe the presence of the drug or its active metabolites in human milk, and its bioavailability to the breastfed child
Females and Males of Reproductive Potential	• Pregnancy testing • Contraception • Infertility

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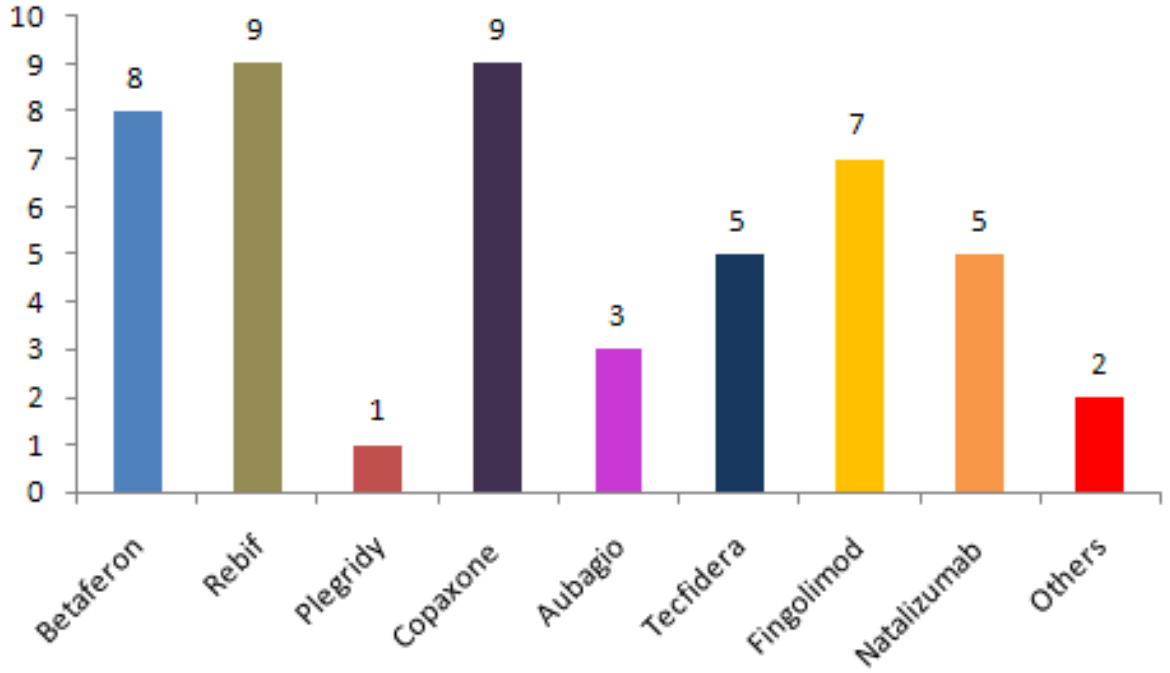
1. Content and format of labeling for human prescription drug and biological products; requirements for pregnancy and lactation labeling. *Fed Regist.* 2014;79(233):72063-72103. To be codified at 21 CFR Part 201; 2. FDA Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products - Content and Format . Guidance for Industry. December 2014.

DMTs before pregnancy



65% (71% first line) were treated with DMTs before pregnancy

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Glatiramer acetate

- Studies in animals have not shown reproductive toxicity. Current data on pregnant women indicate no malformative or feto/neonatal toxicity of Copaxone. To date, no relevant epidemiological data are available. As a precautionary measure, it is preferable to avoid the use of COPAXONE during pregnancy unless the benefit to the mother outweighs the risk to the fetus
- COPAXONE® is no longer contraindicated during pregnancy

1. Food and Drug Administration (FDA) (2014) Content and format of labeling for human prescription drug and biological products; requirements for pregnancy and lactation labeling. Available from: http://www.federalregister.gov/a/2014-28241. Accessed 26 November, 2016
2. MHRA - Medicine & Health products Regulatory Agency. (2016) Summary of product characteristics,Copaxone 20mg/ml Solution for Injection, pre-filled Syringe, revision 02/12/2016
3. MHRA - Medicine & Health products Regulatory Agency (2017) Summary of product characteristics,Copaxone 40mg/ml Solution for Injection, pre-filled Syringe, revision 30/03/2017

Pregnancy and fetal outcomes after interferon-β exposure in multiple sclerosis

MS Study Group of the Italian Neurological Society.

- Women who discontinued IFN-β <4 weeks from conception (exposed) were compared with those who were not exposed (never received IFN-β or discontinued it ≥4 weeks before conception)
- 396 pregnancies in 388 women (88 exposed to treatment)
- IFN-β exposure: not associated with an increased risk of spontaneous abortion (95% CI: 0.4 to 2.9, p = 0.88); associated with both lower baby weight (p < 0.0001) and length (p < 0.0001).
- In exposed patients the proportion of spontaneous abortion was within the expected range for the Italian population
- No significant fetal complications, malformations, or developmental abnormalities observe in the exposed group over a median follow-up of 2.1 years.

Amato et al. Neurology 2010

Teriflunomide (Aubagio): pregnancy, and fertility

- Women of child-bearing potential must use reliable contraception
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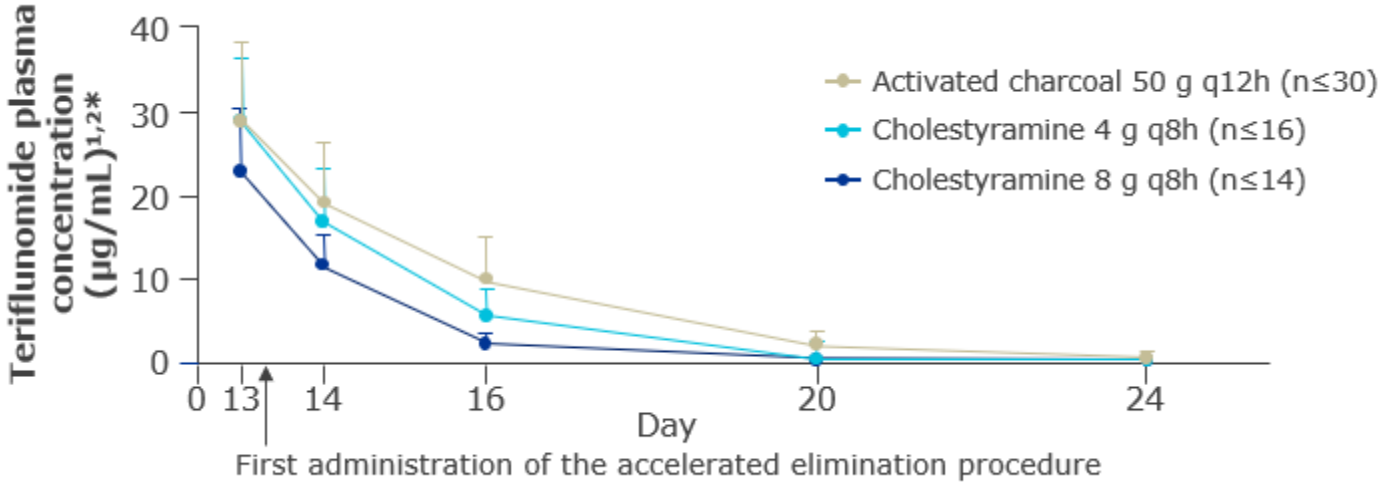

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Aubagio Prescribing Information, 2012 . 1. Kieseier B, Benamor M. *Neurol Th*er 2014;3:133-8. 2. Kieseier B et al. ACTRIMS–ECTRIMS 2014, Poster P846. 3. Hellwig K et al. EAN 2015,

Dimethyl fumarate (Tecfidera):pregnancy, and fertility

- Pregnancy
  - No or limited data from use of dimethyl fumarate in pregnant women
  - Tecfidera is not recommended during pregnancy and in women of childbearing potential not using appropriate contraception
  - Tecfidera should be used during pregnancy only if clearly needed and if the potential benefit justifies the potential risk to the foetus
- Fertility
  - No data on effects of Tecfidera on human fertility
  - Data from preclinical studies do not suggest an increased risk of reduced fertility

Tecfidera (Dimethyl fumarate): Summary of Product Characteristics (EMA), 2014

Natalizumab

- No difference in major malformations, low birth weight, or premature births in MS women exposed to natalizumab respect with MS women without DMT exposure and healthy women [1, 2]
- Newborns may experience transient hematologic abnormalities including anemia and trombocitopenia in women using Natalizumab during the last trimester of the pregnancy[3]
- Risk of discontinuation before the pregnancy is associated not only for a return of disease activity, but also rebound activity [4]
- It has been suggested one could justify no washout, since monoclonal antibodies do not cross the placenta until the second trimester; in case of increased disease activity even during pregnancy, the risk-benefit ratio favours maintenance of natalizumab treatment should discussed with the patient.[5]

1 Ghandy et al.Expert Opin Biol Ther 2016; 2 Friend S et al. BMC Neurol 2016; 3 Haghikia A et. JAMA Neurol 2016; 4 De Giglio L et al. Acta Neurol Scand 2015; Amato MP et al. Neurol Sci 2017

Pregnancy outcomes in the clinical development programme of fingolimod in multiple sclerosis

Karlsson G, Francis G, Koren G, Heining P, Zhang X, Cohen JA, Kappos L, Collins W.

- Pregnancy outcomes reported from phase II, phase III, and phase IV clinical studies. Fingolimod exposure defined as treatment at the time of conception or in the 6 weeks before conception.
- 66 pregnancies with in utero exposure to fingolimod: 28 live births, 9 spontaneous abortions, 24 elective abortions, 4 ongoing pregnancies, 1 lost to follow-up
- Malformations: 1 congenital unilateral posteromedial bowing of the tibia and 1 acrania. Elective abortions for 1 case each of tetralogy of Fallot, spontaneous intrauterine death, and failure of foetal development.
- Abnormal foetal development in 5 of 66 pregnancies exposed to fingolimod (in all 5 exposure took place in the first trimester)
- Effective contraception required during treatment. This should be continued for at least 2 months after stopping treatment to eliminate drug from body.

Karlsson et al. Neurology 2014

Alemtuzumab (Lemtrada): pregnancy, and fertility

- Limited amount of data from the use of Lemtrada in pregnant women.
  - Serum concentrations low or undetectable within approx. 30 days following each treatment course.
  - Lemtrada should be administered during pregnancy only if the potential benefit justifies the potential risk to the foetus; may cross the placental barrier and potential risk for foetus.
  - Thyroid disease: increased risk for miscarriage and foetal effects such as mental retardation and dwarfism; transient neonatal Graves' disease.
- Effective contraceptive measures when receiving a course of treatment and for 4 months following that course of treatment. Negative pregnancy test prior to infusion

Lemtrada: Summary of product characteristics. 2013

Cladribine (Mavenclad): pregnancy, and fertility

- Before initiation of treatment both in year 1 and year 2, women of childbearing potential and males who could potentially father a child should be counselled regarding the potential for serious risk to the foetus and the need for effective contraception.
- Women of childbearing potential must prevent pregnancy by use of effective contraception during cladribine treatment and for at least 6 months after the last dose.
- Women using systemically acting hormonal contraceptives should add a barrier method during cladribine treatment and for at least 4 weeks after the last dose in each treatment year.
- Male patients must take precautions to prevent pregnancy of their female partner during cladribine treatment and for at least 6 months after the last dose.

Pregnancy planning[a] with MAVENCLAD® can begin 6 months after completing the final dose in Year 2, while disease control[b] can be sustained for up to 4 years[1]

	Month 1 Week 1	Month 2 Week 1	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12
Year 1	4–5 days[c]	4–5 days[c]	Avoid pregnancy Women who become pregnant under therapy with MAVENCLAD® should discontinue treatment									
Year 2	4–5 days[c]	4–5 days[c]										
Year 3	Pregnancy planning opportunity[1]											
Year 4												

Each treatment week consists of 4 or 5 days on which a patient receives 10mg or 20mg (one or two tablets) as a single daily dose, depending on body weight.

Following completion of 2 treatment courses, no further MAVENCLAD® treatment is required in Years 3 and 4[1]

The treatment effects of MAVENCLAD® can be sustained despite the drug being rapidly eliminated from the plasma (terminal half-life of <24 hours)[2,4,5]

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1. MAVENCLAD® Argentina Cert. N° 58662, Disp. N°1684/2018, ANMAT approval 2018; 2. Liliemark J. Clin Pharmacokinet 1997;32:120–31; 3. Giovannoni G et al. Mult Scler 2017;doi:10.1177/1352458517727603;
4. Giovannoni G, et al. N Engl J Med 2010;362:416–26;
5. Sigal DS, et al. Blood 2010;116:2884–96.

Ocrelizumab (ocrevus): pregnancy, and fertility

- There is a limited amount of data from the use of ocrelizumab in pregnant women[1]
    - No B-cell count data have been collected in infants exposed to ocrelizumab and the potential duration of B-cell depletion in infants is unknown[1]
- The EU SmPC states that women of child bearing potential should use contraception while receiving ocrelizumab and for 12 months after the last infusion of ocrelizumab[1]

1. OCREVUS EU SmPC, January 2018.

Treatment of relapses during the pregnancy

- Intravenous prednisone, prednisolone and methylprednisolone are moderately safe in the second and third trimesters of pregnancy for the treatment of serious acute exacerbations
- There is controversy about whether steroid exposure in the first trimester is associated with cleft lip and palate abnormalities, but many obstetricians feel short-term steroids can be used safely in all trimesters
- Plasmapherese is not contraindicated by pregnant women
- Immunoglobulins are not contraindicated by pregnant women

Cree, Mult Scler 2013

UK consensus on pregnancy in multiple sclerosis

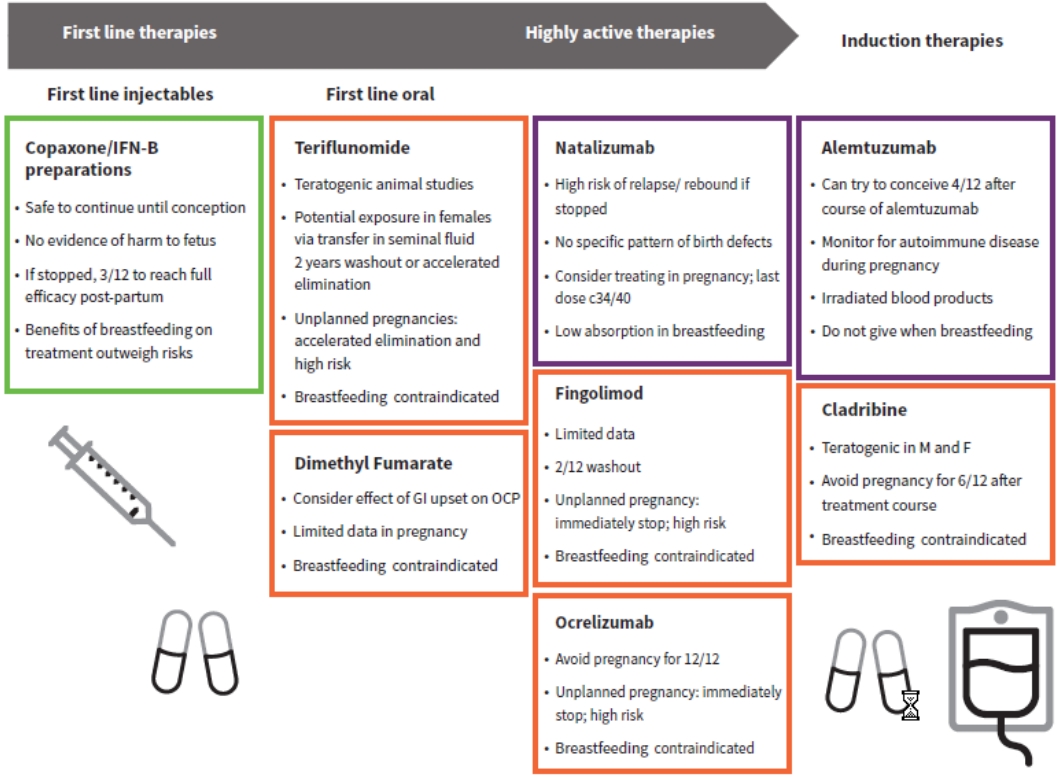

Figure 2 Infographic summarising advice about the use of disease-modifying drugs during pregnancy and in breastfeeding. IFN-B, interferon beta.

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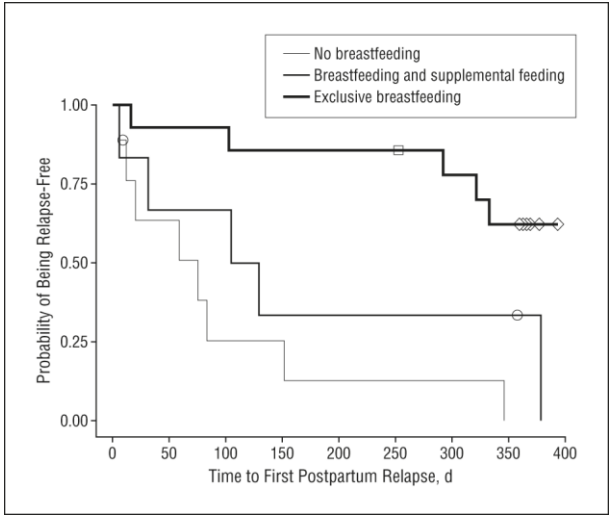
Dobson R, et al. Pract Neurol 2019;**0:1–9.**Pregnancy and MS

Symptomatic therapies

Category B	Category C	Category D	Category X
Oxybutynin	Baclofen	Benzodiazepine	
Pemoline	Tizanidine	Phenytoin	
Sildenafil	Dantrolene		
	Fluoxetine		
	Carbamazepine		
	Gabapentin		
	Isoniazide		
	Loperamide		
	Propranolol		
	Aminopyridine		
	Tolterodine		

Exclusive breastfeeding and the risk of postpartum relapses in women with multiple sclerosis

- 32 pregnancies in women with MS prospectively followed up and 29 age-matched healthy controls:[1]
  - Exclusive breastfeeding (breastfeeding for at least 2 months after delivery): 69%
  - Exclusive breastfeeding and concomitant suppression of menses significantly reduced the risk of postpartum relapses (adjusted HR=7.1; 95%CI 2.1–24.3; p=0.002)
  - Pre-pregnancy RR and use of DMDs were not predictive of postpartum relapses
- Decrease in interferon-γ producing CD4+T-cells was associated with postpartum relapses and normalized during breastfeeding[2]



Kaplan-Meier curve for multiple sclerosis relapses in the postpartum period comparing women with different breastfeeding choices. Frequency and timing of postpartum relapses: similar among women with MS who did not breastfeed exclusively to those who did not breastfeed; exclusive breastfeeding significantly reduced the risk of postpartum relapses.[1]

Reproduced with permission from Archives in Neurology[1,2]

[1]Langer-Gould et al. Arch Neurol 2009; 2Langer-Gould et al. Arch Neurol 2010

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Conclusions

- MS primarily affects women of childbearing age
- MS-related symptoms may affect the ability to conceive and impact the family planning decision making process
- Pregnancy has not been shown to adversely affect disease progression in women with MS
- Relapse rates decline during pregnancy, most markedly in the third trimester
- MS is not related to an increased risk of cesarean section and low birth weight

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Conclusions

- There is no increase in birth defects, perinatal mortality or adverse fetal outcomes
- MS does not appear to increase the risk of abortion, pre-term delivery, or pre-eclampsia

- MS is not related to a condition of ‘high risk’ pregnancy

- Optimal conception timing is very important

- When to stop DMT and when to start require an exhaustive plan

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Thank you

Professor Carlo Pozzilli
Professor Maura Pugliatti
Professor Celia Oreja-Guevara

Breastfeeding and disease-modifiying treatment

	Elimination half-life	Lactation category*
Glatiramer acetate	~ 20 h	L3
IFN B (IM)	~ 10 h	L3
IFN B (SC)	69 ± 37 h	L3
IFNB 1b	8 min – 3 h	L3
Fingolimod	6 – 9 days	L4
Natalizumab	11 ± 4 days	L3

More information about treatments and breastfeeding: www.e-lactancia.org

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* Lactation risk categories are currently not listed in drug package inserts; DMT classifications based on lactation risk as L1 (safest), L2 (safer), L3 (moderately safe), L4 (possibly hazardous) or L5 (contraindicated)

Houtchens & Kolb, J Neurol 2013

Effect of MS Symptoms During Pregnancy

Fatigue

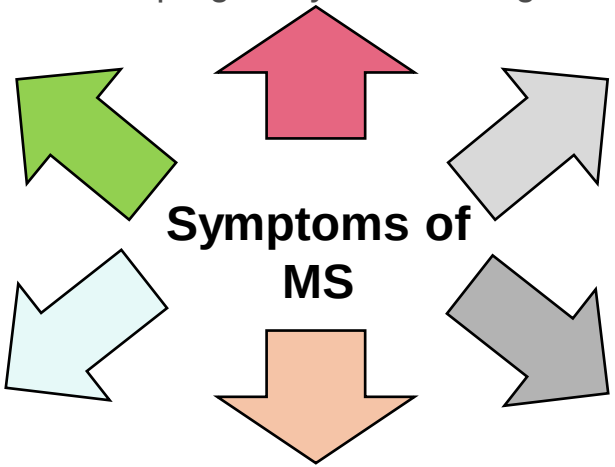
- MS-related fatigue may augment natural pregnancy-related fatigue

Depression

- Discontinuation of antidepressants during pregnancy is associated with a relapse of depressive symptoms

Cognitive Impairment

- May negatively impact relationships and the ability to perform daily activities



Anxiety

- Expectation of worsening MS symptoms, financial issues, and the need for support postpartum may exacerbate anxiety

Bladder and Bowel Dysfunction

- Increased risk for developing urinary tract infections (UTIs)[1,2]
- Increased incidence of constipation[3]

Mobility

- Incoordination and muscle weakness may alter balance and lead to falls4
- Increased risk of deep vein thrombosis if bedridden or wheelchair bound

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*1. Dahl J, et al. *J Neurol.* 2005;65:1961-3; 2. Chen YH, et al. *Mult Scler.* 2009;15:606-12; 3. National MS Society. Pregnancy, delivery, and the post partum period- information for women to share with their physicians [handout]. 2006;

Agents for MS approved

Approved agent	Old Categories
IFN-β	C
Glatiramer acetate	B
Fingolimod	C
Natalizumab	C
Mitoxantrone	D
Alemtuzumab	C
Monoclonal anti-CD20	C
BG-12	C
Daclizumab	C
Teriflunomide	X

Breastfeeding is not related to postpartum relapses in multiple sclerosis

The Italian Pregnancy Dataset:

- 302 of 423 pregnancies in 298 women with MS resulted in full-term deliveries
- Followed up for at least 12 months after delivery
- In the multivariate analysis, only relapses before (HR 1.5, 95% CI 1.3–1.9, p<0.001) and during pregnancy (HR 2.2, 95%CI 1.5–3.3, p<0.001) predicted postpartum relapses
- No differences in the time dependent profile of relative risk (RR): effect for group x time F= 0.695, p=0.730
- mean RR before during and after pregnancy was significantly lower in the exclusive breastfeeding group (effect for group F=8.297, p=0.004)
- No impact of breastfeeding

Abstract available: https://www.ncbi.nlm.nih.gov/pubmed/21734184
Portaccio et al. Neurology 2011