Pregnancy in MS & NMOSD

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Health

Objectives

- Review bi-directional influences of MS/NMOSD and pregnancy
- Review counseling for women of childbearing age with MS and NMOSD
  - Pre-pregnancy period
  - Pregnancy period
  - Post-partum period

Counseling Timelines

- ***Pre-pregnancy period***
  - Contraception
  - Fertility
  - DMT safety
  - Wash-out of DMTs, if needed
- ***Pregnancy period***
  - Treatment of relapses, if occurs
  - Delivery methods
  - Anesthesia/analgesia
- ***Post-partum period***
  - Relapse rate and treatment if relapse occurs, follow-up visits
  - Breast-feeding, if so desired
  - Re-introduction of DMTs

Multiple Sclerosis

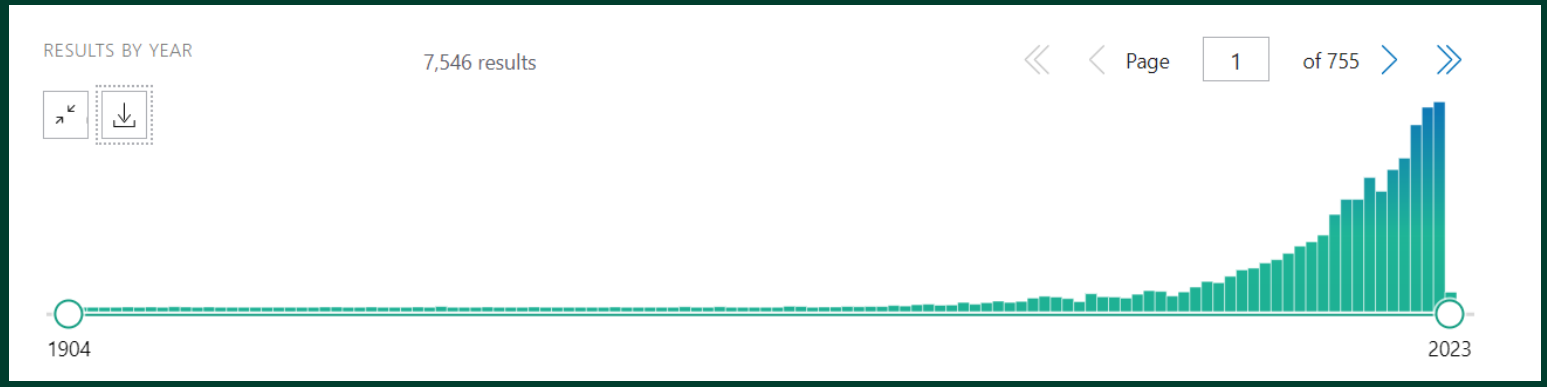
Pre-pregnancy

- 31-year-old woman diagnosed with RRMS, no children, recently married. Not on birth control. Comes in for the first visit.
- Counseling
  - *Starting a DMT*
  - *Contraception*
  - *Fertility*
  - *Pregnancy*

- Dr., I heard that patients with MS should not have children?
- I would like to have a child; will my MS be ok during pregnancy?
- Will I have a relapse when I am off medications?

MS & Pregnancy

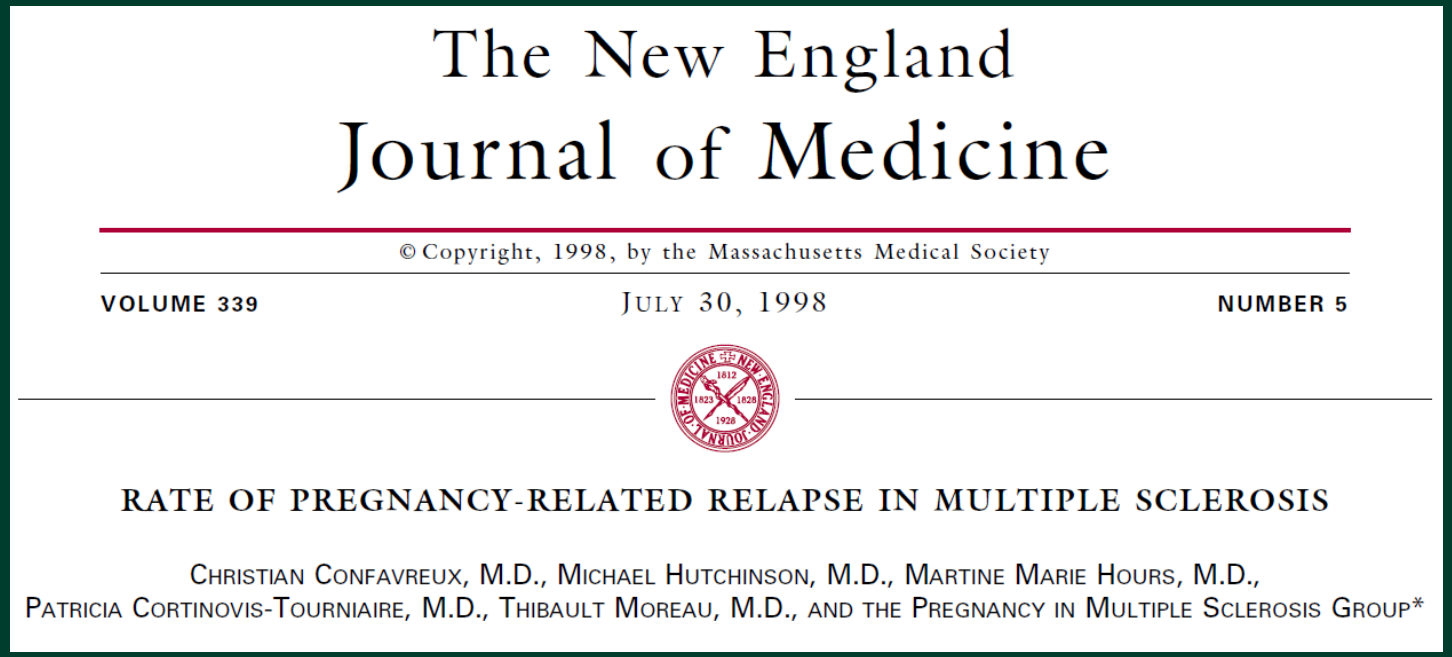
- The influence of pregnancy on the course of multiple sclerosis (MS) had been debated until 1998
- Before the 1990's Women with MS (WWMS) were typically discouraged from having children
- Counseling of WWMS has changed dramatically



Pubmed MS and pregnancy 1904-2023

The Pregnancy in MS Study (PRIMS)

- 254 women with relapsing MS
- Prospective study, 12 European countries
- Compare ARR pre-conception year to pregnancy and post-partum (2 years)



The New England
Journal of Medicine

VOLUME 339 JULY 30, 1998 NUMBER 5

RATE OF PREGNANCY-RELATED RELAPSE IN MULTIPLE SCLEROSIS

CHRISTIAN CONFAVREUX, M.D., MICHAEL HUTCHINSON, M.D., MARTINE MARIE HOURS, M.D.,
PATRICIA CORTINOVIS-TOURNIAIRE, M.D., THIBAULT MOREAU, M.D., AND THE PREGNANCY IN MULTIPLE SCLEROSIS GROUP*

PRIMS

- During the 3rd trimester compared to the year prior to pregnancy, 70% decrease
- Increase in "4th" trimester
  - 28% of pts had relapse
  - ARR returns to pre-pregnancy
- No change in disability progression

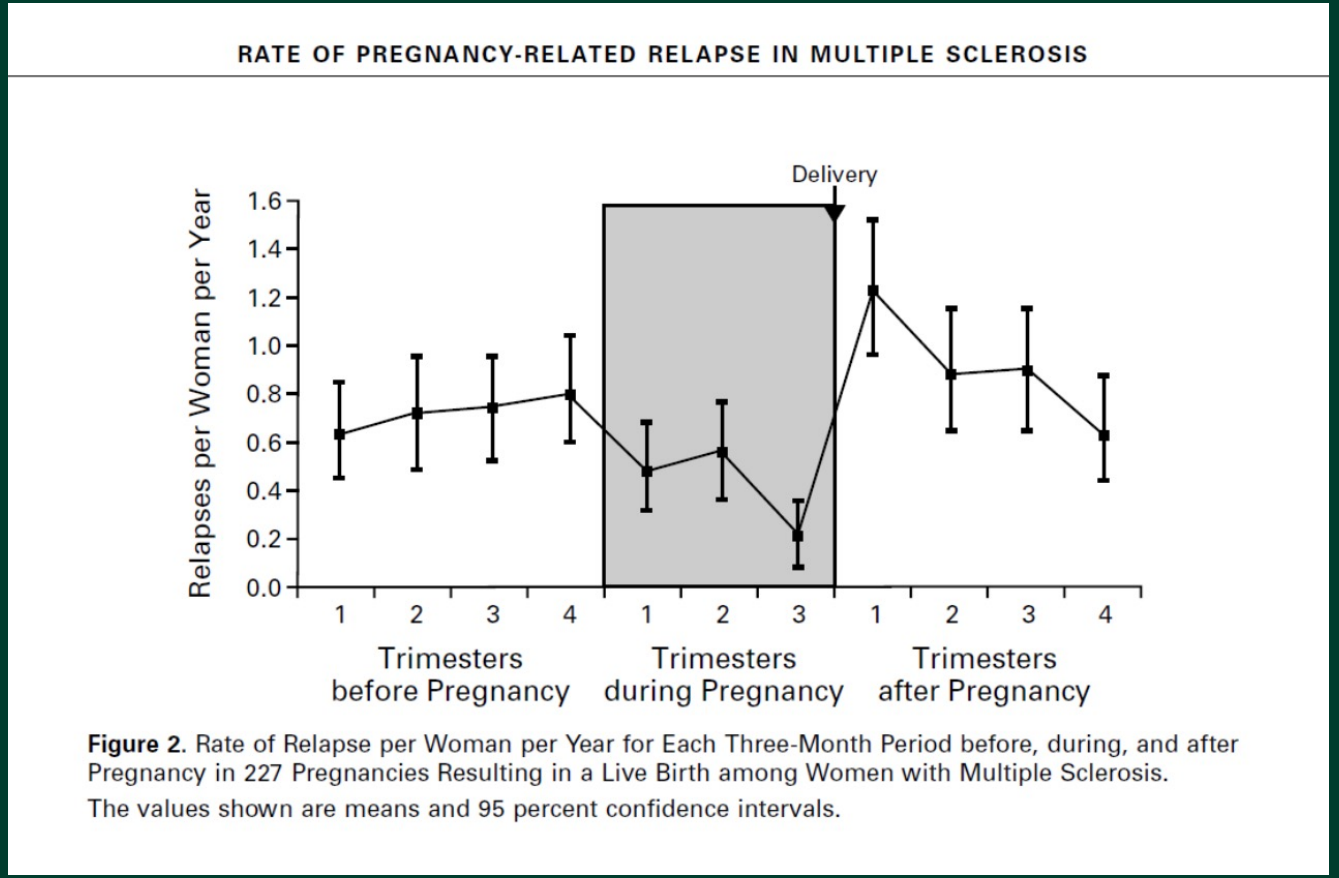


Figure 2. Rate of Relapse per Woman per Year for Each Three-Month Period before, during, and after Pregnancy in 227 Pregnancies Resulting in a Live Birth among Women with Multiple Sclerosis. The values shown are means and 95 percent confidence intervals.

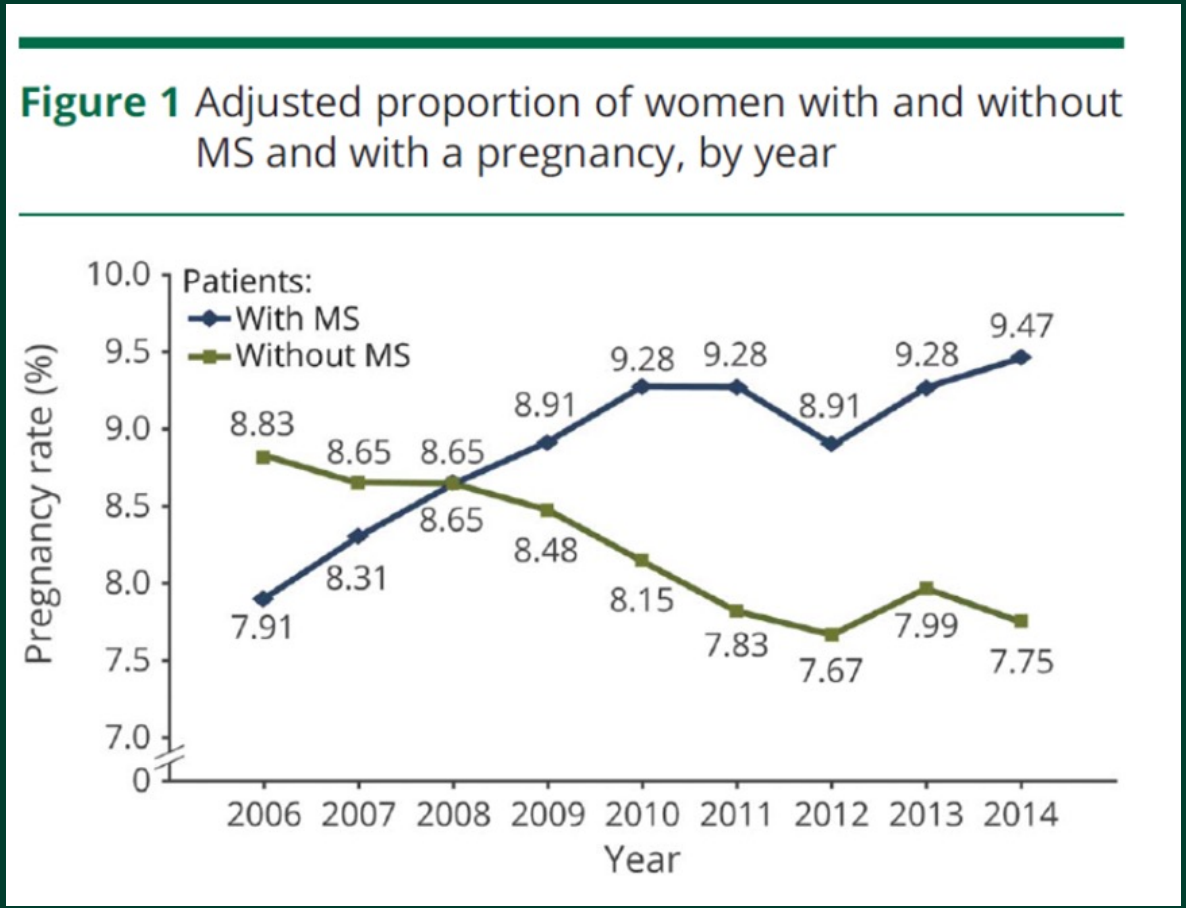
Confavreux C, et al. Rate of pregnancy-related relapse in multiple sclerosis. Pregnancy in Multiple Sclerosis Group. N Engl J Med. 1998 Jul 30;339(5):285-91.

Pregnancy Influence on MS

- Estrogen, human chorionic gonadotropin (HCG), and progesterone trigger changes in the lymphocytic response profile.
- There is suppression of T-Helper 1 (TH1) response
  - Reducing the release of interferon gamma and tumor necrosis factor alpha
- Pregnancy-associated down-regulation of cell-mediated immunity
- Immune system is induced by estrogen and other sex hormones
  - Shift to Th2 (anti-inflammatory cytokines) rather than Th1 (pro-inflammatory cytokines)
    - Involved in maternal immune tolerance toward the presence of the fetus

Lamaita et al. Multiple Sclerosis in Pregnancy and its Role in Female Fertility: A Systematic Review. JBRA Assist Reprod. 2021 Jul 21;25(3):493-499

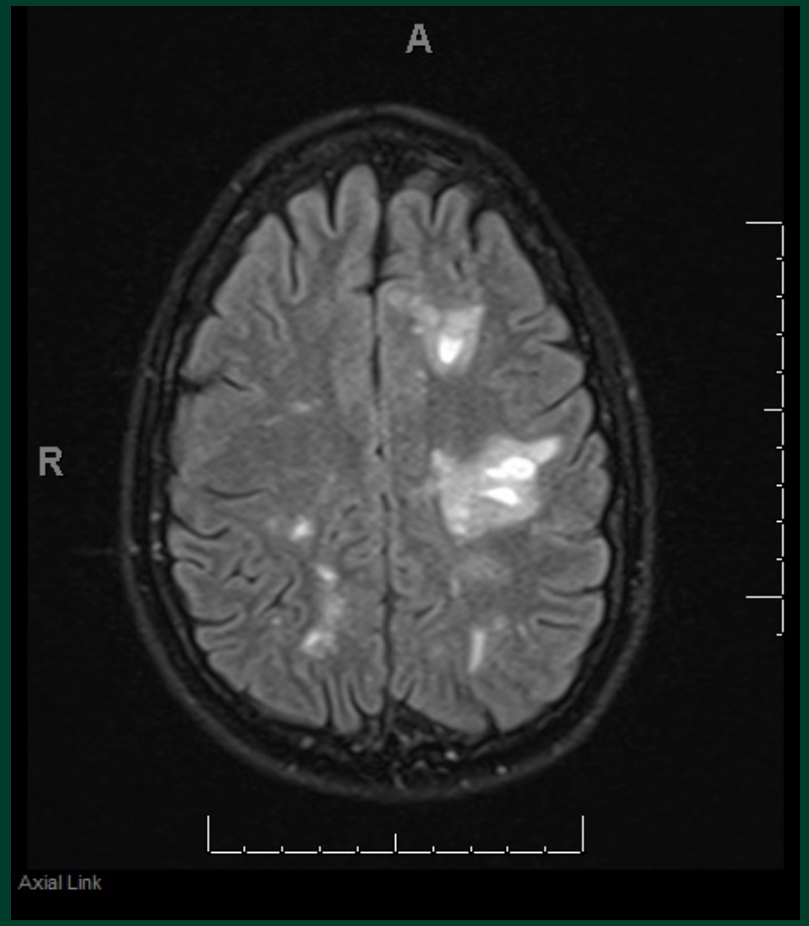
Pregnancy Rates in WWMS

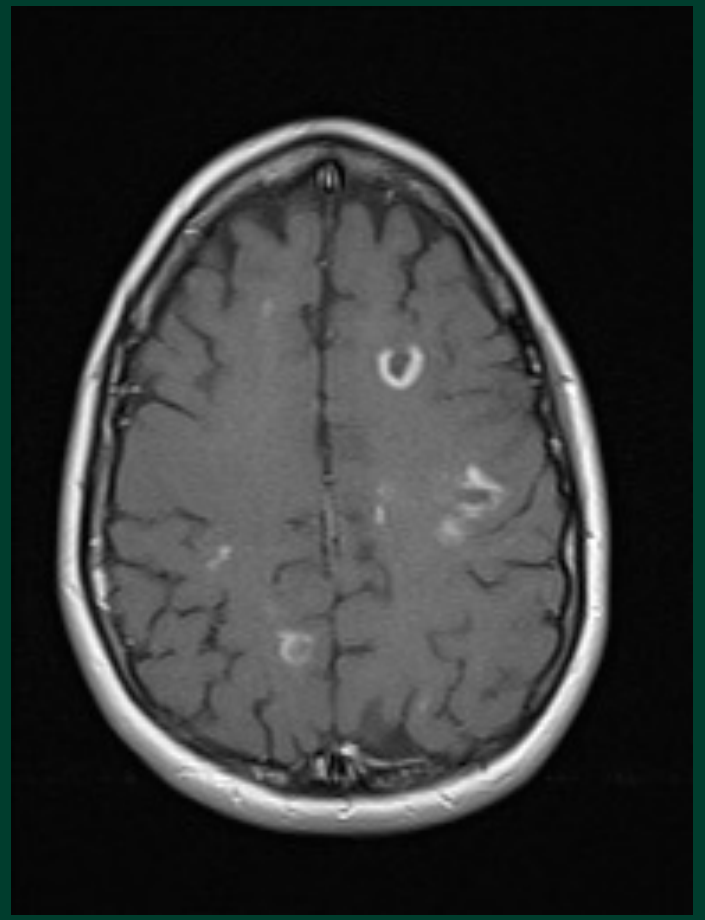


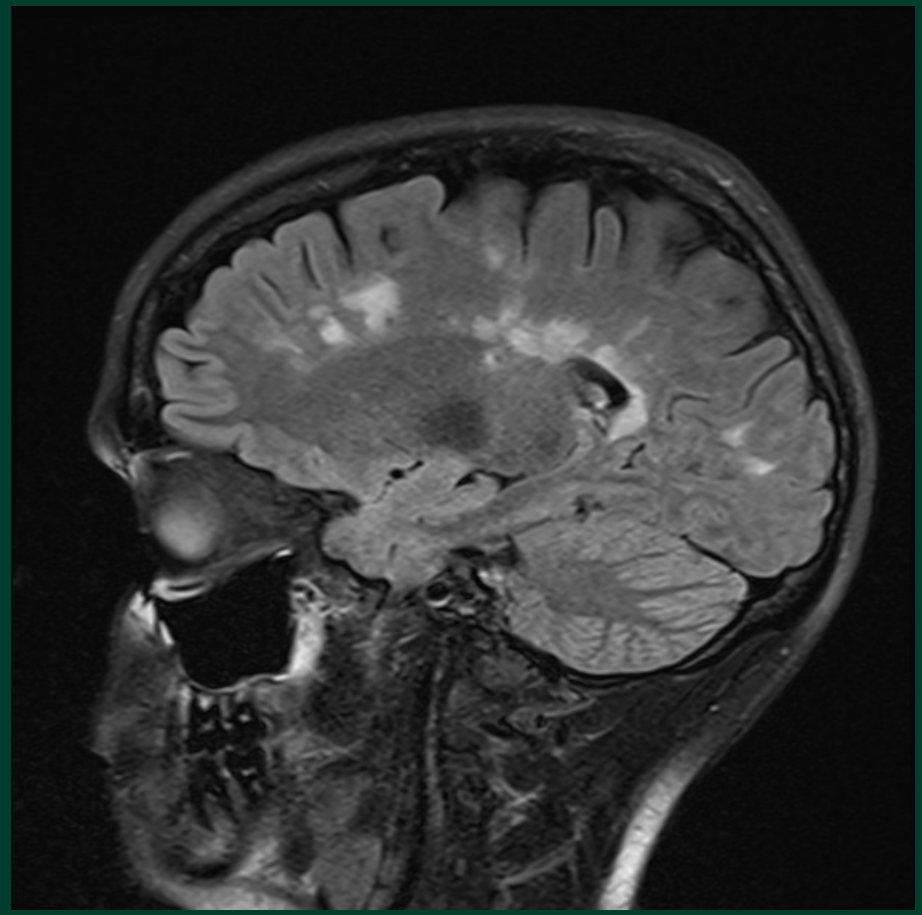
- Retrospective US administrative claims study
- From 2006 to 2014 change in pregnancy rates for both WWMS and women w/o MS

Houtchens MK, et al. Pregnancy rates and outcomes in women with and without MS in the United States. Neurology. 2018 Oct 23;91(17).

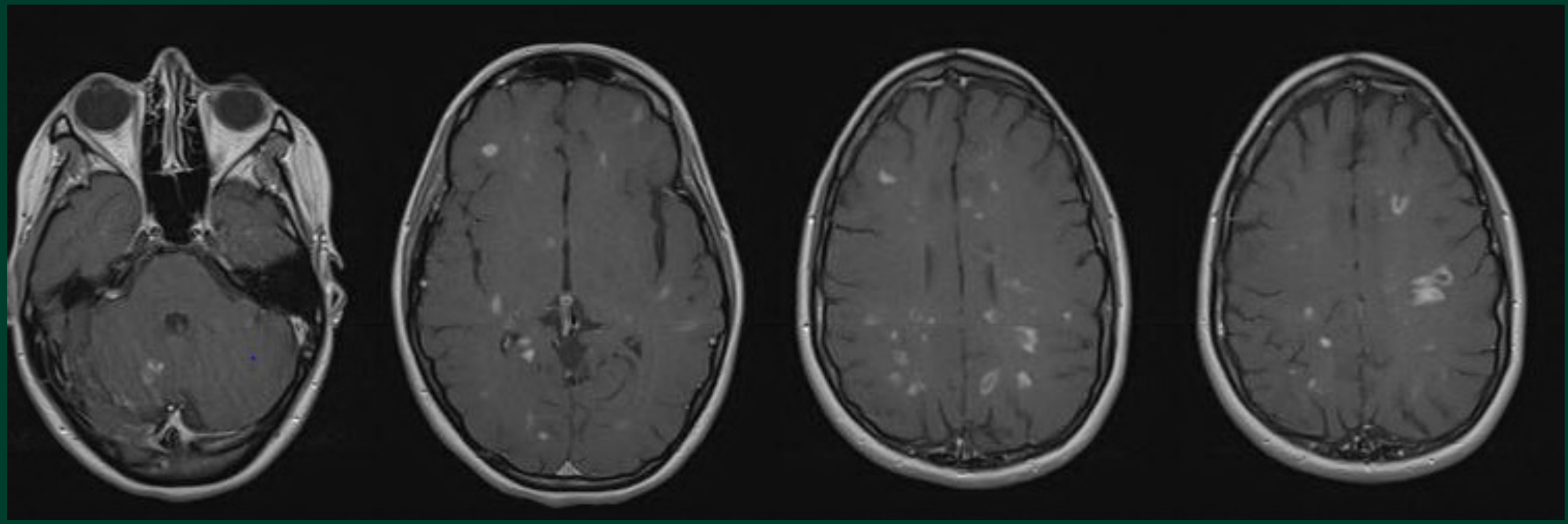
Case : MRI







Case: MRI



Case :

- Significant radiological burden
- Clinically, doing well
- Recommend start DMT and start birth control

Contraception in Women with MS (WWMS)

- Effective contraception until desired pregnancy
- DMTs in general, not safe in pregnancy, reminder at each visit
- Most contraceptives are safe for MS patients
- **Modafinil** – may reduce the efficacy of OCP
- **Teriflunomide** increases some OCP hormone levels
- Combined hormonal contraceptives are to be used with caution in pts with prolonged immobility
- Potentially teratogenic medications – dictate highly effective methods

Effectiveness of Family Planning Methods

Most Effective

Less than 1 pregnancy per 100 women in a year

6-12 pregnancies per 100 women in a year

18 or more pregnancies per 100 women in a year

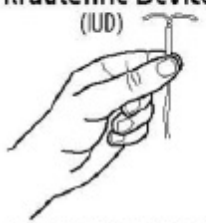
Least Effective

Reversible

Implant

0.05 %*

Intrauterine Device (IUD)



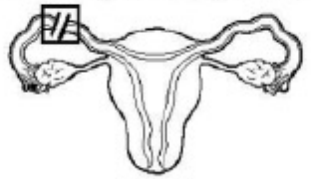
LNG - 0.2 % Copper T - 0.8 %

Permanent

Male Sterilization (Vasectomy)

0.15 %

Female Sterilization (Abdominal, Laparoscopic, Hysteroscopic)

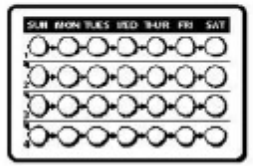


0.5 %

Injectable

6 %

Pill



9 %

Patch

9 %

Ring

9 %

Diaphragm

12 %

Male Condom

18 %

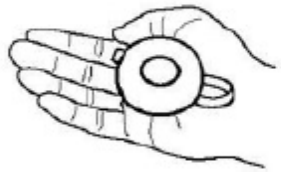
Female Condom

21 %

Withdrawal

22 %

Sponge

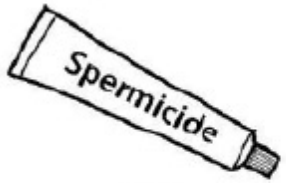


24 % parous women
12 % nulliparous women

Fertility-Awareness Based Methods

24 %

Spermicide



28 %

*The percentages indicate the number out of every 100 women who experienced an unintended pregnancy within the first year of typical use of each contraceptive method.

How to make your method most effective

After procedure, little or nothing to do or remember.

Vasectomy and hysteroscopic sterilization: Use another method for first 3 months.

Injectable: Get repeat injections on time.

Pills: Take a pill each day.

Patch, Ring: Keep in place, change on time.

Diaphragm: Use correctly every time you have sex.

Condoms, sponge, withdrawal, spermicides: Use correctly every time you have sex.

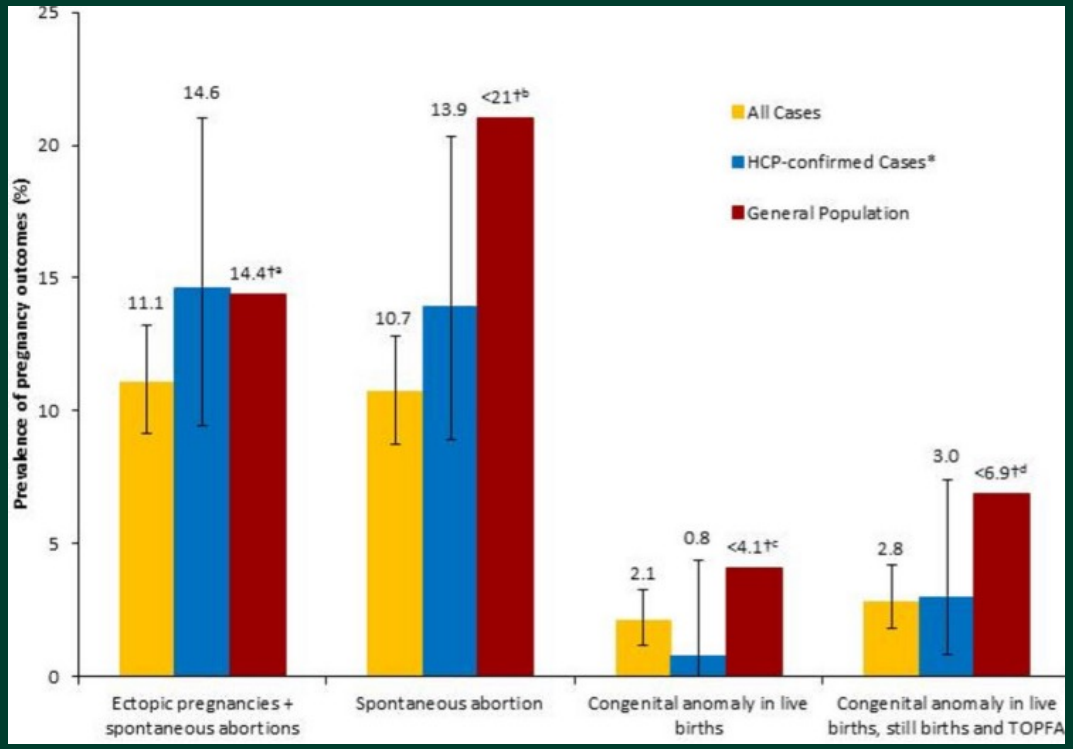
Fertility awareness-based methods: Abstain or use condoms on fertile days. Newest methods (Standard Days Method and TwoDay Method) may be the easiest to use and consequently more effective.

DMT selection

- Individualized care –
  - Desire for children – *timing, birth control methods?*
  - Disease severity
    - Clinical – ARR, disability - *cognitive / physical disabilities*
    - Radiological – *disease burden and activity/ enhancing lesions*
  - Individual DMT – *risk of stopping vs continuation of DMT*
  - Discuss risk/benefit – *to mother/child*
  - Shared decision making with patient
  - In general, all DMTs are stopped during pregnancy

Interferon beta

- Approved 1993
- Large molecules
- Extensive data > 3000 pregnancies
- No increase spontaneous abortions or congenital abnormalities
- Systematic review - lower birth weight and preterm deliveries
- No washout required
- Safe to BF - interferon in breast milk found 0.006% of the maternal dose



Lu E, et al. Disease-modifying drugs for multiple sclerosis in pregnancy: a systematic review. Neurology. 2012 Sep 11;79(11):1130-5.
Hellwig K, et al. European Interferon-beta Pregnancy Study Group. Pregnancy outcomes in interferon-beta-exposed patients with multiple sclerosis: results from the European Interferon-beta Pregnancy Registry. J Neurol. 2020 Jun;267(6):1715-1723.
Hale TW, Siddiqui AA, Baker TE. Transfer of interferon β-1a into human breastmilk. Breastfeed Med. 2012 Apr;7(2):123-5.

Glatiramer acetate and generic formulations

- Approved 1996
- Large molecule
- Extensive data
- Data in humans safe with early exposure
- “Category B”
- No increase in fetal abnormalities
- No washout, stop at positive pregnancy test or continue throughout pregnancy

Herbstritt S, et al. Glatiramer acetate during early pregnancy: A prospective cohort study. Mult Scler. 2016 May;22(6):810-6.
Canibaño B, et al. Pregnancy-related issues in women with multiple sclerosis: an evidence-based review with practical recommendations. J Drug Assess. 2020 Jan 23;9(1):20-36.

Sphingosine-1-phosphate receptor modulators

- Approved 2010
- (fingolimod 2010, siponimod 2019, ozanimod 2020, ponesimod 2021,)
- Small molecule, crosses placenta
- **Do not use during pregnancy or breastfeeding, washout - 2 months**
- S1P receptor is involved in organogenesis of blood vessels and heart
- **CAUTION** - Rebound disease –12 w to 24 w post-discontinuation
  - Start other DMT to prevent rebound
- If first trimester exposure – stop and refer for US & high-risk OB

Geissbühler Y, et al. Evaluation of pregnancy outcomes in patients with multiple sclerosis after fingolimod exposure. Ther Adv Neurol Disord. 2018 Nov 3;11:1756286418804760.
Meinl I, Havla J, Hohlfeld R, Kümpfel T. Recurrence of disease activity during pregnancy after cessation of fingolimod in multiple sclerosis. Mult Scler. 2018 Jun;24(7):991-994.
Karlsson G, et al. Pregnancy outcomes in the clinical development program of fingolimod in multiple sclerosis. Neurology. 2014 Feb 25;82(8):674-80.
https://www.novartis.us/sites/www.novartis.us/files/gilenya.pdf

Teriflunomide

- Approved 2012
- Small molecule
- **Do not use in pregnancy or breastfeeding**
- Animals linked to teratogenicity (none in humans)
- ½ life = 15-18 days, (8 mo to 2 years) due to enterohepatic recycling
  - Use effective contraception until levels of drug are below 0.02 mg/L
  - Accidental pregnancy – use accelerated elimination
  - Data from pregnancy registries and post-marketing do not show teratogenic signals

Kieseier BC, Benamor M. Pregnancy outcomes following maternal and paternal exposure to teriflunomide during treatment for relapsing-remitting multiple sclerosis. Neurol Ther. 2014 Nov 20;3(2):133-8.
Andersen JB, Moberg JY, Spelman T, Magyari M. Pregnancy Outcomes in Men and Women Treated With Teriflunomide. A Population-Based Nationwide Danish Register Study. Front Immunol. 2018 Nov 23;9:2706.
Vukusic S, et al. Pregnancy outcomes in patients with multiple sclerosis treated with teriflunomide: Clinical study data and 5 years of post-marketing experience. Mult Scler. 2020 Jun;26(7):829-836.

Dimethyl fumarate (and other fumarates)

- Approved 2013
- Small molecule
- Short half life
- No human evidence of fetotoxicity
- No washout recommended

Gold R, et al. Delayed-Release Dimethyl Fumarate and Pregnancy: Preclinical Studies and Pregnancy Outcomes from Clinical Trials and Postmarketing Experience. Neurol Ther. 2015 Dec;4(2):93-104.

Vaughn C, Bushra A, Kolb C, Weinstock-Guttman B. An Update on the Use of Disease-Modifying Therapy in Pregnant Patients with Multiple Sclerosis. CNS Drugs. 2018 Feb;32(2):161-178

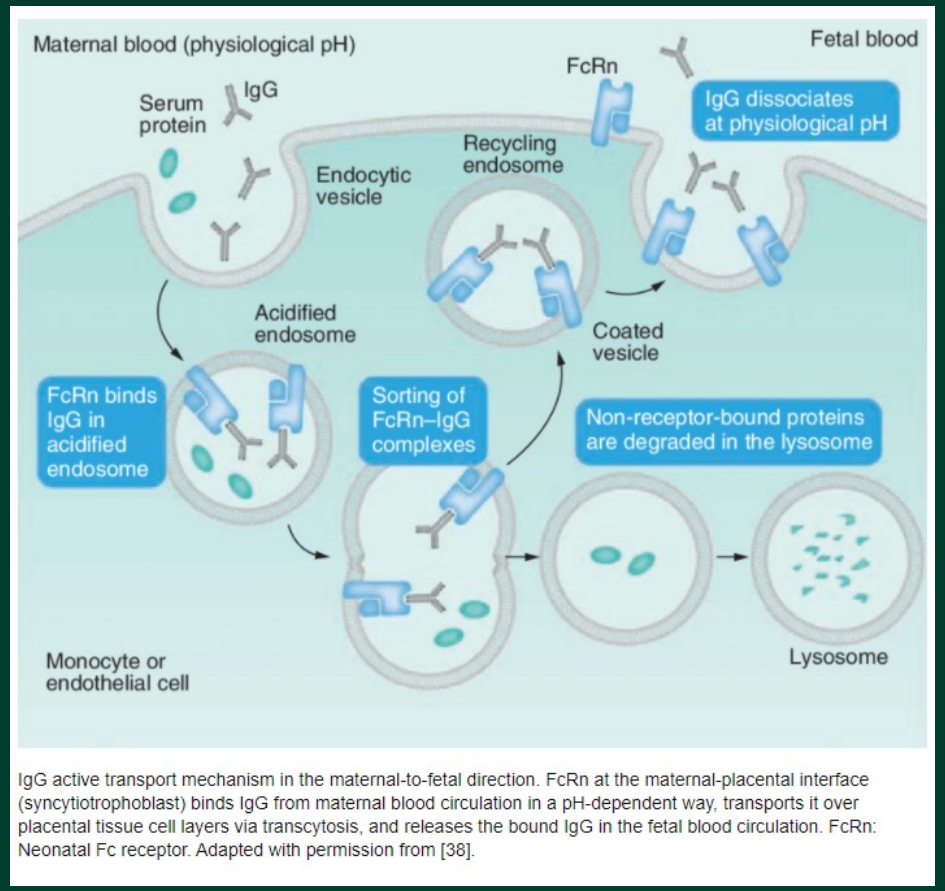
Natalizumab

- Approved 2004
- Monoclonal IgG4
- In general, **do not use in pregnancy or breastfeeding**
- 8.3% major or minor malformations w/o pattern
- Wash out **~ 2 months vs stop at conception**
- **High risk of rebound** (8-16 weeks post discontinuation)
  - Switch therapy before conception to prevent rebound
- First trimester exposure – consider extended dosing (Q6-8 weeks), must stop @34 weeks and monitor child blood counts if in utero-exposure
  - High risk OB – screen for pancytopenia, liver dysfunction

Demortiere S, et al. Maintenance of natalizumab during the first trimester of pregnancy in active multiple sclerosis. Mult Scler. 2021 Apr;27(5):712-718.
Friend S, et al. Evaluation of pregnancy outcomes from the Tysabri® (natalizumab) pregnancy exposure registry: a global, observational, follow-up study. BMC Neurol. 2016 Aug 24;16(1):150.
Portaccio E, et al. MS Study Group of the Italian Neurological Society. Pregnancy decision-making in women with multiple sclerosis treated with natalizumab: I: Fetal risks. Neurology. 2018 Mar 6;90(10):e823-e831.

B-cell therapies

- Large monoclonal antibodies
- FDA recommends 6 mo and EMA recommends 12 mo - washout
- IgG transfer across placenta is minimal in 1st trimester, increases significantly around weeks 13–18, and peaks around 22–26 weeks GA.
- Transient B-cell depletion in infants - check infant b-cells
  - Vaccine timing for infants



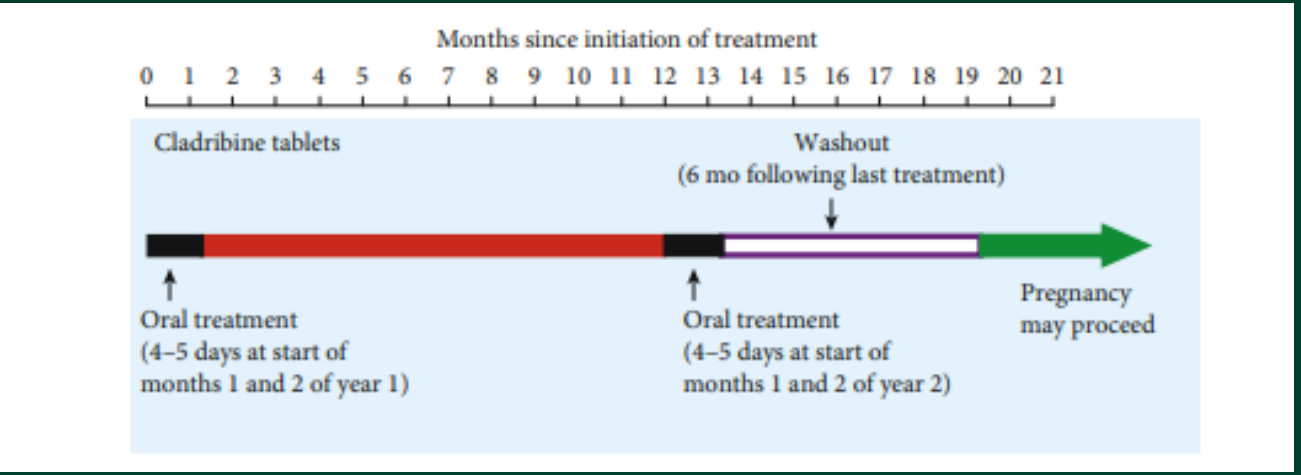
IgG active transport mechanism in the maternal-to-fetal direction. FcRn at the maternal-placental interface (syncytiotrophoblast) binds IgG from maternal blood circulation in a pH-dependent way, transports it over placental tissue cell layers via transcytosis, and releases the bound IgG in the fetal blood circulation. FcRn: Neonatal Fc receptor. Adapted with permission from [38].

Malek A. Role of IgG antibodies in association with placental function and immunologic diseases in human pregnancy. Expert Rev Clin Immunol. 2013 Mar;9(3):235-49.

Pregnancy outcomes in patients treated with ocrelizumab
ECTRIMS Online Library. Oreja-Guevara C. 09/12/19; 279140; P780

Cladribine

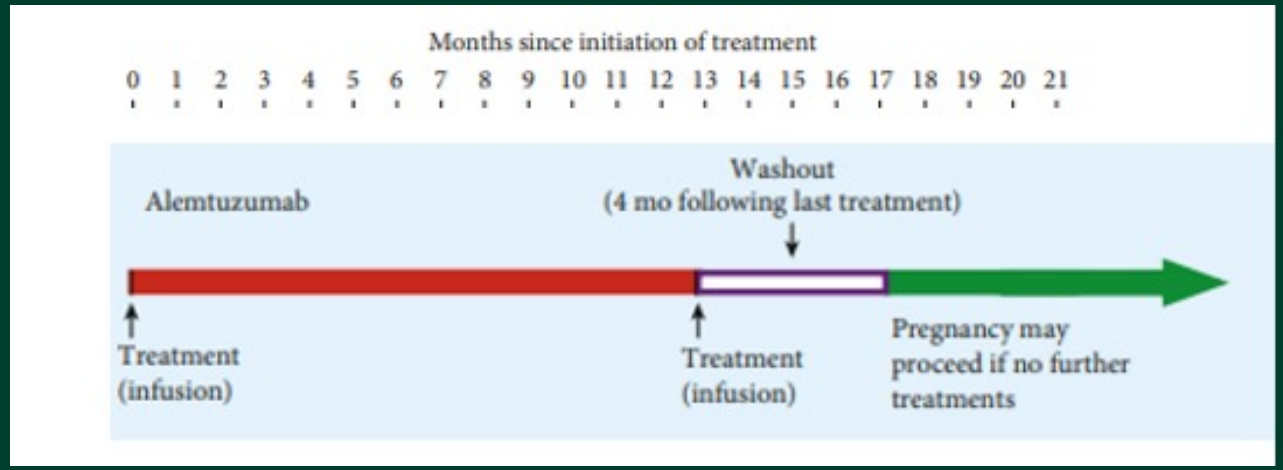
- Approved 2019
- Small molecule
- Avoid conception for **6 months** post last dose
- Do not breastfeed during or one week post treatment



Al Jumah M, et al. Family Planning for People with Multiple Sclerosis in Saudi Arabia: an Expert Consensus. Mult Scler Int. 2021 Feb 15;2021:6667006.

Alemtuzumab

- Approved 2014
- Monoclonal antibody
- Avoid conception for **4 months**
- Do not use during breastfeeding
- Caution in mother as high risk of autoimmune disorders – ie thyroid



Case

- DMT selection
- 2 years clinically and radiologically stable
- Stops DMT to become pregnant
- Unable to conceive after 6 months
  - Next steps?

Fertility

- MS patients generally have normal fertility
- However, studies have shown an increase in assistive reproductive technology in MS, (up to 5 times higher)
- Referral to fertility specialist, earlier than non-MS pts
- *Likely multifactorial:*
  - Purposeful delay
  - Sexual dysfunction, decreased libido
  - Endometriosis
  - Lower levels of antimullerian hormone, less follicles & smaller ovaries *uncontrolled pts
    - *There was no difference in women with controlled MS or without the disease*

Correale J, et al. Increase in multiple sclerosis activity after assisted reproduction technology. Ann Neurol. 2012 Nov;72(5):682-94.

Factors that may discourage pregnancy

- Functional and cognitive impairment and their impacts on childcare
- Fear of pregnancy triggering the progression of the disease
- Risk transmitting the disease to offspring
- The impact of the disease on gestational risk

Ghafoori F, et al. Pregnancy and Motherhood Concerns Surrounding Women with Multiple Sclerosis: A Qualitative Content Analysis. Int J Community Based Nurs Midwifery. 2020 Jan;8(1):2-11.

PREGNANCY PERIOD

Will my pregnancy be high risk?

- Pregnancy Outcomes
- A higher proportion of women with MS than without had claims for: (n= 2,115 per group)
  - premature labor (31.4% vs 27.4%; p = 0.005)
  - infection (13.3% vs 10.9%; p = 0.016)
  - neurologic complications (1.6% vs 0.6%; p = 0.005)
  - acquired fetal damage (27.8% vs 23.5%; p = 0.002)
  - congenital fetal malformations (13.2% vs 10.3%; p = 0.004)

Houtchens MK, Edwards NC, Schneider G, Stern K, Phillips AL. Pregnancy rates and outcomes in women with and without MS in the United States. Neurology. 2018 Oct 23;91(17):e1559-e1569.

Managing relapses during pregnancy

- MRI is ok during pregnancy and post partum period
- Gadolinium crosses the placenta – avoid during pregnancy
- Avoidance of steroids in the first trimester - risk of fetal malformation
- Steroids 2nd and 3rd if needed
- Plasma exchange if needed

Cox JL, Koepsell SA, Shunkwiler SM. Therapeutic plasma exchange and pregnancy: A case report and guidelines for performing plasma exchange in a pregnant patient. J Clin Apher. 2017 Jun;32(3):191-195.

POST-PARTUM PERIOD

What are my chances of having a relapse?

- Clinical predictors of post-partum relapse (24 months PP)
  - ARR returned to pre-pregnancy values
  - Postpartum relapses associated with:
    - Higher ARR in the pre-pregnancy year
    - Higher relapse rate during pregnancy
    - Higher EDSS at pregnancy onset
    - *Neither epidural analgesia nor breast-feeding was predictive*
  - 72% of the women did not relapse during this period

Vukusic S, et al. Pregnancy In Multiple Sclerosis Group. Pregnancy and multiple sclerosis (the PRIMS study): clinical predictors of post-partum relapse. Brain. 2004 Jun;127(Pt 6):1353-60.

Studies following PRIMS

- The postpartum rebound was found to be less pronounced than what was observed in the PRIMS study
  - Up to ~50% less than in PRIMS
  - PP ARR lower in DMT exposed group
  - One study showed, pre-conception DMT ~45% reduction in PP relapse
  - Relapse rate during pregnancy was associated with long washout periods before conception
  - Less risk if natalizumab was stopped at pregnancy confirmation vs one month prior

Hellwig K, et al. Multiple sclerosis and pregnancy: experience from a nationwide database in Germany. Ther Adv Neurol Disord. 2012 Sep;5(5):247-53.
Hughes SE, et al. MSBase study group. Predictors and dynamics of postpartum relapses in women with multiple sclerosis. Mult Scler. 2014 May;20(6):739-46.
Alroughani R, et al. Relapse occurrence in women with multiple sclerosis during pregnancy in the new treatment era. Neurology. 2018 Mar 6;90(10).

What if I have a relapse during pregnancy or post-partum ?

- Rule out pseudorelapse (UTIs common in pregnancy)
- MRI, if needed – avoid gadolinium during pregnancy
- Post-partum – BF, less than 0.1% of gad is in breast milk
  - "Pump and dump"

  Steroids
  - Pregnancy - should be avoided in first trimester
  - Breastfeeding – discard for 4 hours post dose

Puac P, Rodríguez A, Vallejo C, Zamora CA, Castillo M. Safety of Contrast Material Use During Pregnancy and Lactation. Magn Reson Imaging Clin N Am. 2017 Nov;25(4):787-797
Boz C, et al. Safety of IV pulse methylprednisolone therapy during breastfeeding in patients with multiple sclerosis. Mult Scler. 2018 Aug;24(9):1205-1211.
Bandoli G, et al. A Review of Systemic Corticosteroid Use in Pregnancy and the Risk of Select Pregnancy and Birth Outcomes. Rheum Dis Clin North Am. 2017 Aug;43(3):489-502

Is there something I can do to prevent a post-partum relapse?

- **IVIG**
  - Contradicting data in retro/prospective studies
- **Corticosteroids**
  - 1-gram monthly x 6 months – decreased ARR compared to historical control
- **Hormonal therapy (POPARTMUS)** - Prevention of Post Partum Relapses with Progestin and Estradiol in MS
  - Randomized, prospective - hormonal vs placebo = no difference (n 202)

Achiron A, et al. Effect of intravenous immunoglobulin treatment on pregnancy and postpartum-related relapses in multiple sclerosis. J Neurol. 2004 Sep;251(9):1133-7.
Haas J, Hommes OR. A dose comparison study of IVIG in postpartum relapsing-remitting multiple sclerosis. Mult Scler. 2007 Aug;13(7):900-8.
de Seze J, et al. Intravenous corticosteroids in the postpartum period for reduction of acute exacerbations in multiple sclerosis. Mult Scler. 2004 Oct;10(5):596-7.
Avila-Ornelas J, Avila M, Stosic M, et al. The role of postpartum intravenous corticosteroids in the prevention of relapses in multiple sclerosis. *Int J MS Care*. 2011;13(2):91-93.
Vukusic S, et al. Oral nomegestrol acetate and transdermal 17-beta-estradiol for preventing post-partum relapses in multiple sclerosis: The POPARTMUS study. Mult Scler. 2020 Dec 3.

Will I be able to breastfeed?

- Increasing data on the health benefits of BF for both mom & baby
- No evidence that BF increases PP relapse
- 47% decrease in post-partum relapse rate in those who breast-fed
- Population was diverse
  - Exclusive BF and some mixed
  - Pre-pregnancy MS activity
  - DMT use pre-pregnancy

Pakpoor J, et al. Breastfeeding and multiple sclerosis relapses: a meta-analysis. J Neurol. 2012 Oct;259(10):2246-8.

Bove RM, Houtchens MK. Pregnancy Management in Multiple Sclerosis and Other Demyelinating Diseases. Continuum (Minneap Minn). 2022 Feb 1;28(1):12-33.

Disease-modifying therapy	Description	Detectable in breast milk?	Transluminal transfer?[b]	Possible effects with infant exposure[c]	Compatible with lactation?
Large molecules					
Glatiramer acetate	Large molecule (4.7–13 kDa) heterogeneous strings of amino acids	Not done, unlikely	Yes, as with any amino acid	None	Yes
Interferon beta	Large molecule, protein	0.0006% relative infant dose	Exceedingly low	Flulike symptoms	Yes
Monoclonal antibodies					
Natalizumab	IgG4; 149 kDa	<1:200 of maternal serum level; 2-5% relative infant dose	Low	Infections,[d] impaired vaccine responses or disseminated disease from live vaccines,[d] hepatitis,[d] anemia[d]	Probably
Rituximab	IgG1; 145 kDa	Approximately 1:240 of maternal serum level; <1% relative infant dose	Low	B-cell depletion, infections,[d] impaired vaccine responses or disseminated disease from live vaccines[d]	Probably
Ocrelizumab	IgG1; 145 kDa	Humans not done; monkeys yes	Low	Infections,[d] impaired vaccine responses or disseminated disease from live vaccines,[d] hepatitis,[d] anemia[d]	Probably
Ofatumumab	IgG1; 146 kDa	Humans not done; animals not reported	Low	Infections,[d] impaired vaccine responses or disseminated disease from live vaccines,[d] hepatitis,[d] anemia[d]	Probably

Disease-modifying therapy	Description	Detectable in breast milk?	Transluminal transfer?[b]	Possible effects with infant exposure[c]	Compatible with lactation?
Small molecules					
Dimethyl fumarate	Immediately metabolized to monomethyl fumarate (129 Da), low protein binding	Animals yes/ humans not done but highly likely in high amounts	High	Neurocognitive impairment, lymphopenia, gastrointestinal upset, infections,[d] vaccine responses[d]	No
Sphingosine-1-phosphate (S1P) receptor modulators (fingolimod, ozanimod, ponesimod, siponimod)	Highly protein bound, long half-life	Animals yes/ humans not done but highly likely in low amounts	Moderate	Infections,[d] vaccine responses,[d] cardiovascular effects,[d] pulmonary toxicity,[d] hepatitis[d]	No
Teriflunomide	Inhibits pyrimidine synthesis, highly protein bound, very long half-life	Animals yes/ humans not done but highly likely	High	Pancytopenia, infections, vaccine responses,[d] hepatotoxicity, later-life neoplasms[d]	No
Cladribine	Inhibits nucleoside metabolism, low protein binding, short half-life	Humans not done	High	Lymphopenia,[d] infections,[d] liver injury,[d] later-life neoplasms[d]	No

Bove RM, Houtchens MK. Pregnancy Management in Multiple Sclerosis and Other Demyelinating Diseases. Continuum (Minneap Minn). 2022 Feb 1;28(1):12-33.

Other post-partum considerations

- Depression –post-partum
- Fatigue
- Sleep
- Cognitive changes
- Social stressors
- Bladder and bowel functions

Summary of Pregnancy in MS

- With proper planning and treatment pregnancy is safe for women with MS
- The benefits to the mother must be balanced with the risks to the fetus/child
- Ideally, a treatment plan is laid out prior to conception
- In general MS and pregnancy do not negatively affect one another
- Start discussing birth control and pregnancy early/often

Summary of Pregnancy in MS

- Some DMTs may be harmful to the fetus
- Discontinuation before conception may be warranted; however, stopping treatment might be harmful to the mother
  - Drug registries help with safety profiles
  - Each DMT has its own wash out period
- Breastfeeding must also be discussed and planned

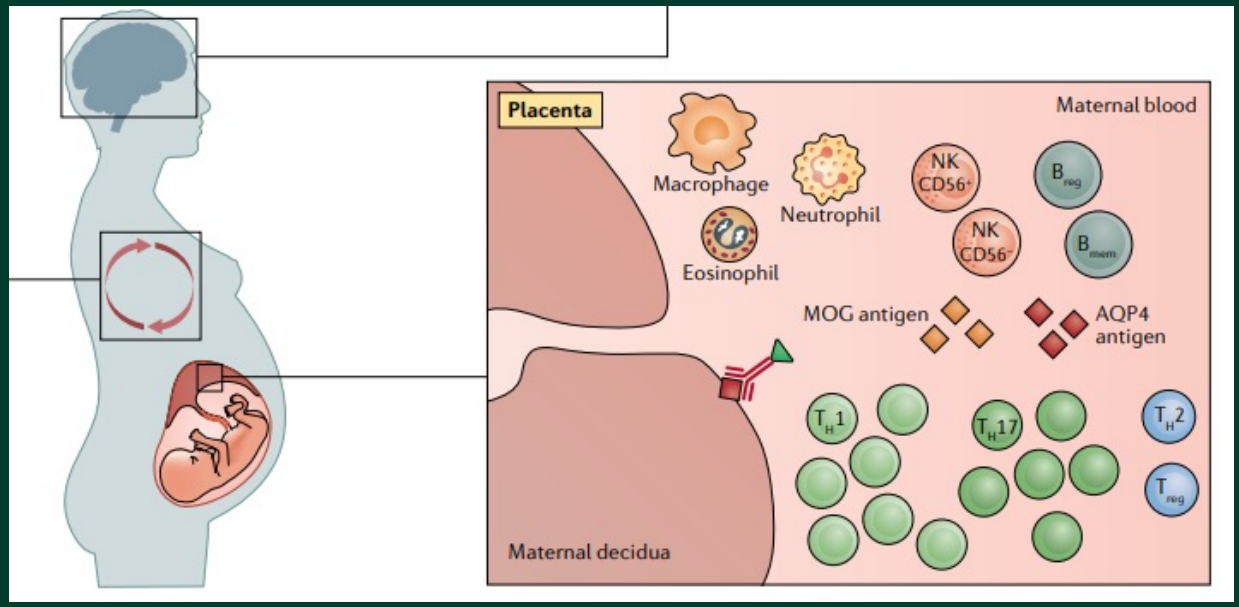
Neuromyelitis Optica Spectrum Disorders

NMOSD and pregnancy

- NMOSD patients should be considered high-risk pregnancy and referred to neurologist and OB with expertise
- Unlike MS, women with NMOSD have an increased rate of pregnancy complications
- NMOSD has been associated with preeclampsia
  - rates of up to 11.5% after disease onset compared with 3.1% in obstetric controls
  - Comorbid autoimmune diseases were noted to be a risk factor for preeclampsia in NMOSD
- NMOSD increases the risk of miscarriage

NMOSD and pregnancy

- Aquaporin-4 (AQP4) is expressed in human placenta
- AQP4-mediated placental inflammation and fetal death in rats
- Miscarriages in NMOSD may be due to the above, likely higher in women with active NMOSD have a high risk of miscarriage
- Co-existing autoimmune disorders also must be considered



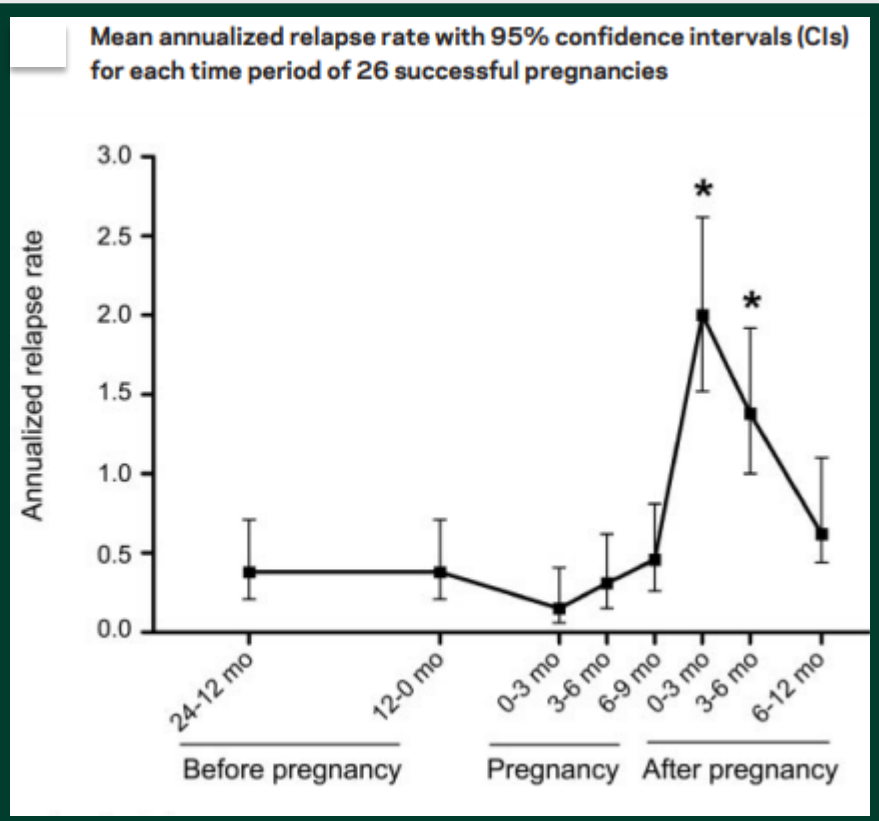
Du Q, Shi Z, Chen H, Zhang Y, Qiu Y, Lang Y, Kong L, Zhou H. Effects of pregnancy on neuromyelitis optica spectrum disorder and predictors of related attacks. Ann Clin Transl Neurol. 2022 Dec;9(12):1918-1925

Mao-Draayer, Y., et al. Neuromyelitis optica spectrum disorders and pregnancy: therapeutic considerations. Nat Rev Neurol ***16,*** *154–170 (2020)*

NMOSD DMTs and pregnancy

- Mycophenolate mofetil, methotrexate, and mitoxantrone should be stopped before conception
- Consideration of safer DMTs azathioprine and monoclonal antibodies, are recommended
- One study reported that only 8.3% of patients with NMOSD receiving anti-CD20 therapy experienced an relapse postpartum

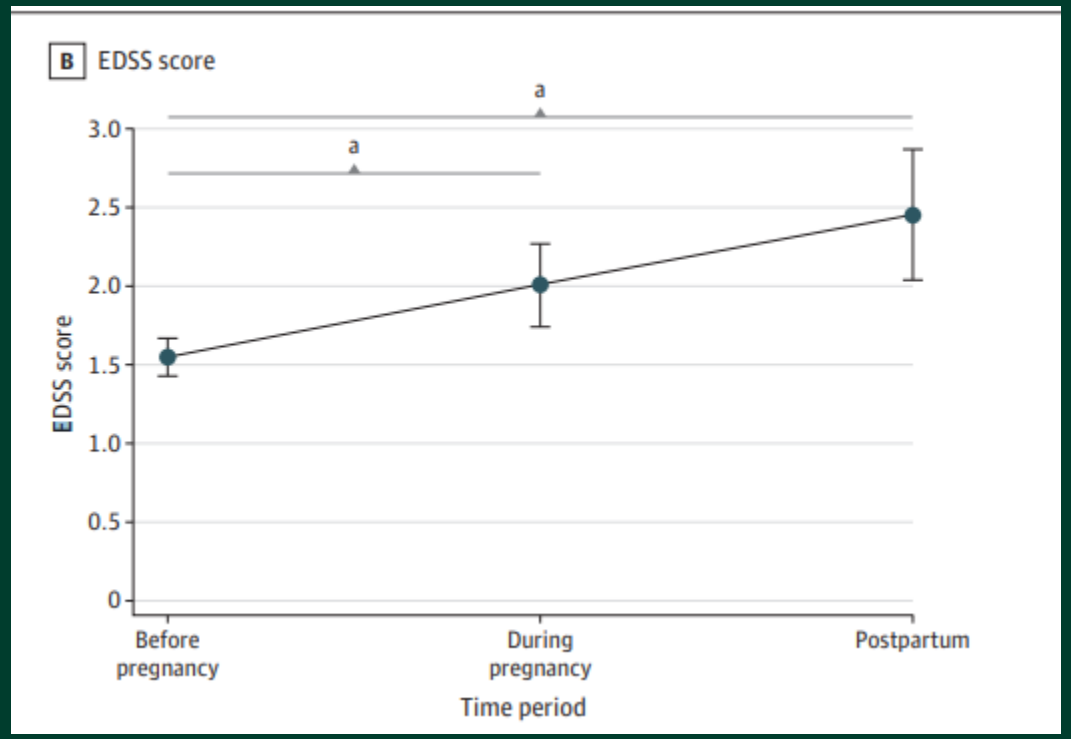
ARR and EDSS scores NMOSD



- Compared to the pre-pregnancy period, ARR was elevated especially during the initial 3 months after delivery
- Immunosuppressive treatment during pregnancy was associated with lower rate of pregnancy-related NMOSD attacks

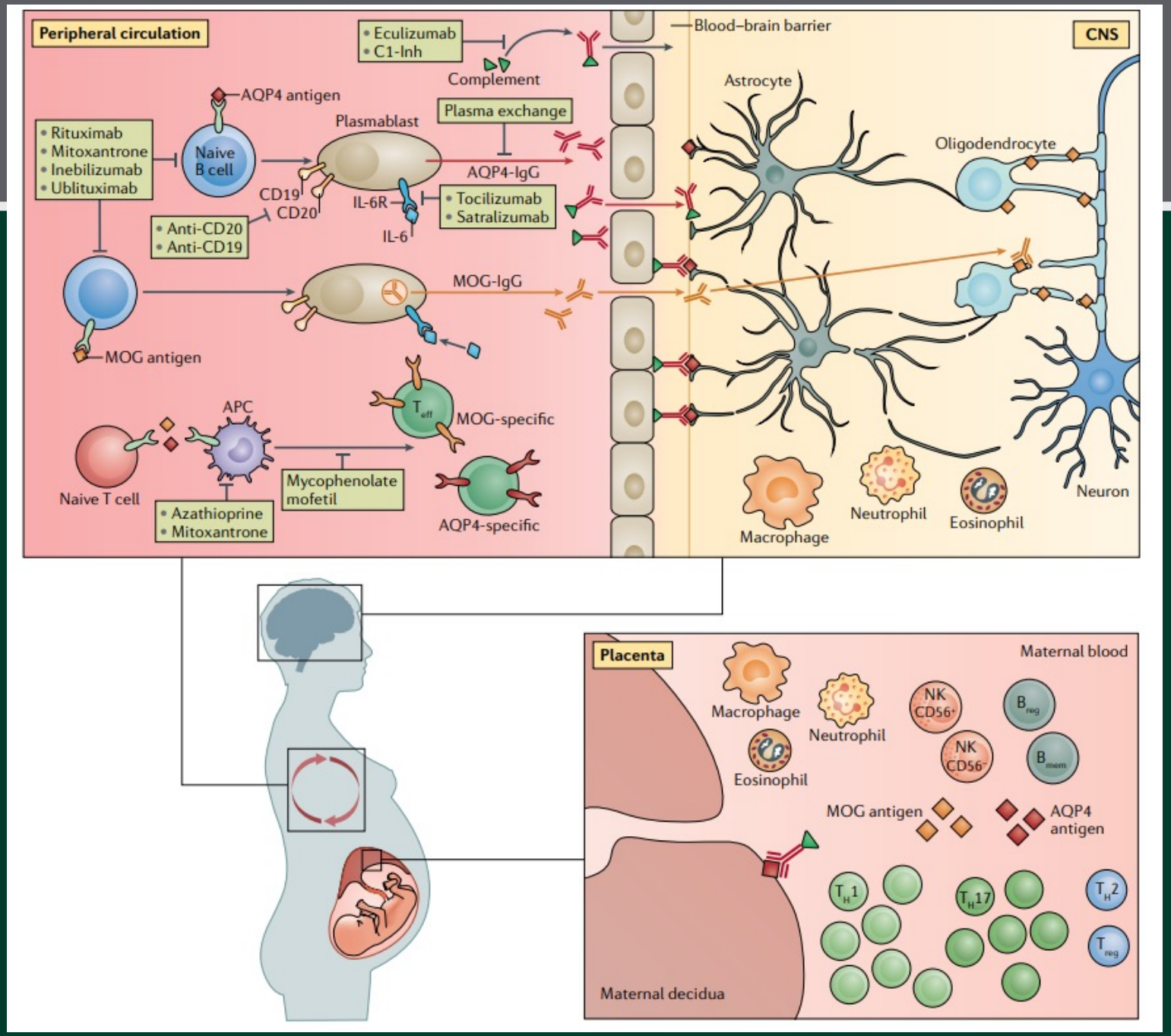
Influence of pregnancy on neuromyelitis optica spectrum disorder
W. Kim, et al. Neurology Apr 2012, 78 (16) 1264-1267.
Wang et al. Analysis of Pregnancy-Related Attacks in Neuromyelitis Optica Spectrum Disorder: A Systematic Review and Meta-Analysis. JAMA Netw Open. 2022 Aug 1;5(8):e2225438.

NMOSD EDSS scores



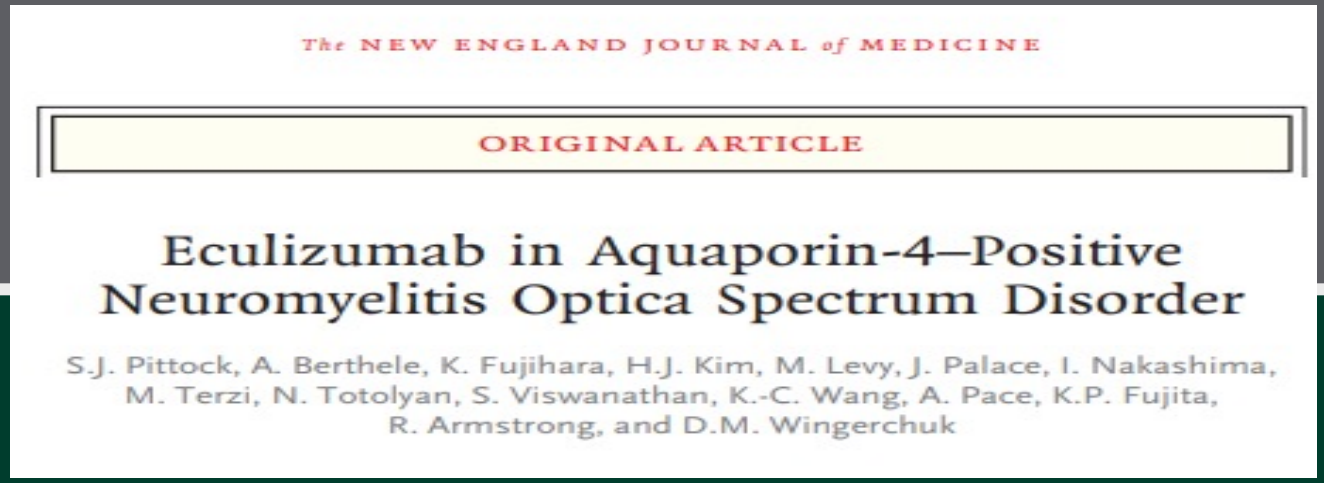
- Systematic review and meta-analysis
  - 443 patients w/ 639 pregnancies
- EDSS score worsened during pregnancy and the postpartum period

Wang et al. Analysis of Pregnancy-Related Attacks in Neuromyelitis Optica Spectrum Disorder: A Systematic Review and Meta-Analysis. JAMA Netw Open. 2022 Aug 1;5(8):e2225438.



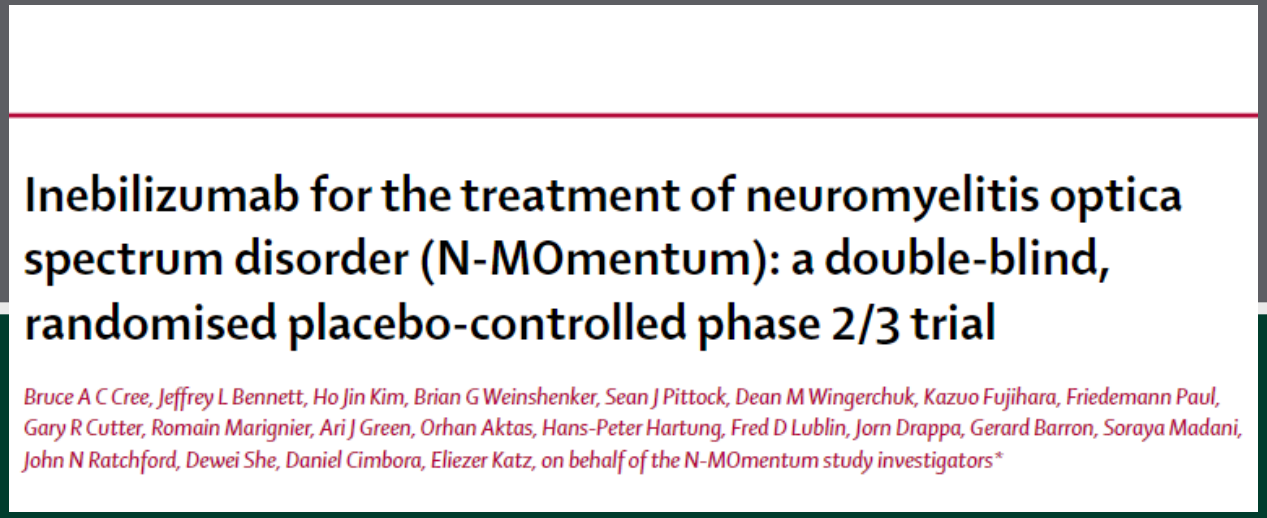
Mao-Draayer, Y., *et al.* Neuromyelitis optica spectrum disorders and pregnancy: therapeutic considerations. *Nat Rev Neurol* **16**, 154–170 (2020)

Eculizumab



- Humanized mAb
- Rapid onset of action -useful for immediate control of active disease
- Inhibits complement cascade by preventing cleavage of C5 complement protein into proinflammatory C5a and C5b, which coordinates the formation of the membrane attack complex
- Wash-out period based on pharmacokinetics – 2 months, but maternal benefit may outweigh risk
- Reassuring safety from paroxysmal nocturnal hemoglobinuria

Inebilizumab

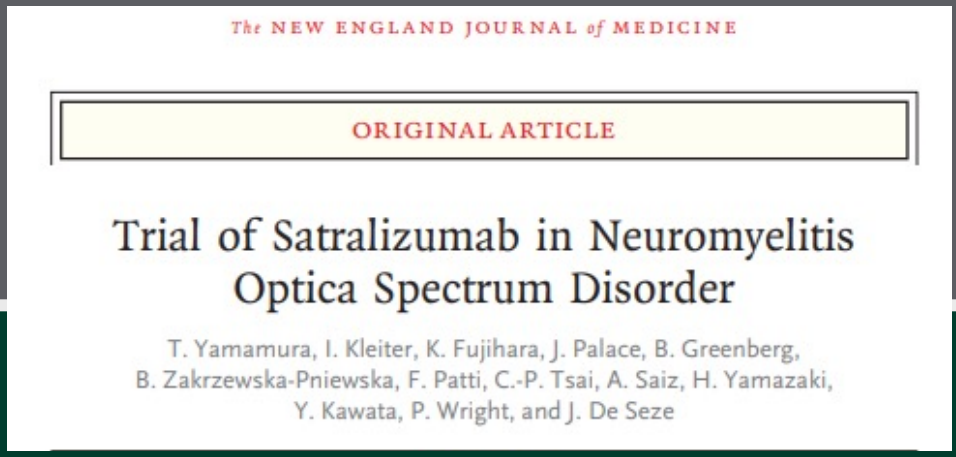


Inebilizumab for the treatment of neuromyelitis optica spectrum disorder (N-MOmentum): a double-blind, randomised placebo-controlled phase 2/3 trial

Bruce A C Cree, Jeffrey L Bennett, Ho Jin Kim, Brian G Weinshenker, Sean J Pittock, Dean M Wingerchuk, Kazuo Fujihara, Friedemann Paul, Gary R Cutter, Romain Marignier, Ari J Green, Orhan Aktas, Hans-Peter Hartung, Fred D Lublin, Jorn Drappa, Gerard Barron, Soraya Madani, John N Ratchford, Dewei She, Daniel Cimbora, Eliezer Katz, on behalf of the N-MOmentum study investigators*

- Humanized, IgG1 monoclonal antibody that binds to the B cell surface marker, CD19
- Similar to other B-cell therapies
- t1/2 18 d (rituximab 18-22 d)
- Per label 6 months, consider less if highly active patient
- Check B-cells in infant and time vaccines as needed

IL-6 inhibitors: satralizumab



- Humanized monoclonal antibody interleukin-6 receptor (IL-6R) antagonist
- Monthly self-injections
- No adverse effects in maternal animals or fetal development
- Wash out – 2 months
- Tocilizumab - in RA no significant increase in risk congenital malformations

Summary of Pregnancy in NMOSD

- With proper planning and treatment pregnancy is possible for women with NMOSD
- The benefits to the mother must be balanced with the risks to the fetus/child
- Ideally, a treatment plan is laid out prior to conception
- Start discussing birth control and pregnancy early/often
- Use of immunosuppressive treatment reduced the risk of pregnancy related relapse
- Most relapses occurred in the first 3 m postpartum

Summary of Pregnancy in NMOSD

- Some DMTs may be harmful to the fetus
- Discontinuation before conception may be warranted; however, stopping treatment might be harmful to the mother and continuation up to conception and beyond may be warranted
  - Drug registries help with safety profiles
  - Each DMT has its own wash out period
- Breastfeeding must also be discussed and planned