



# Gender Differences in Multiple Sclerosis

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# Disclosures

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# Outline

- Impact of sex on MS susceptibility
- Testosterone impact on MS
- Impact of pregnancy on MS disease activity
- MS management strategies: pre-pregnancy, pregnancy & post-partum
- Reproductive aging in MS
- Sexual dysfunction in MS

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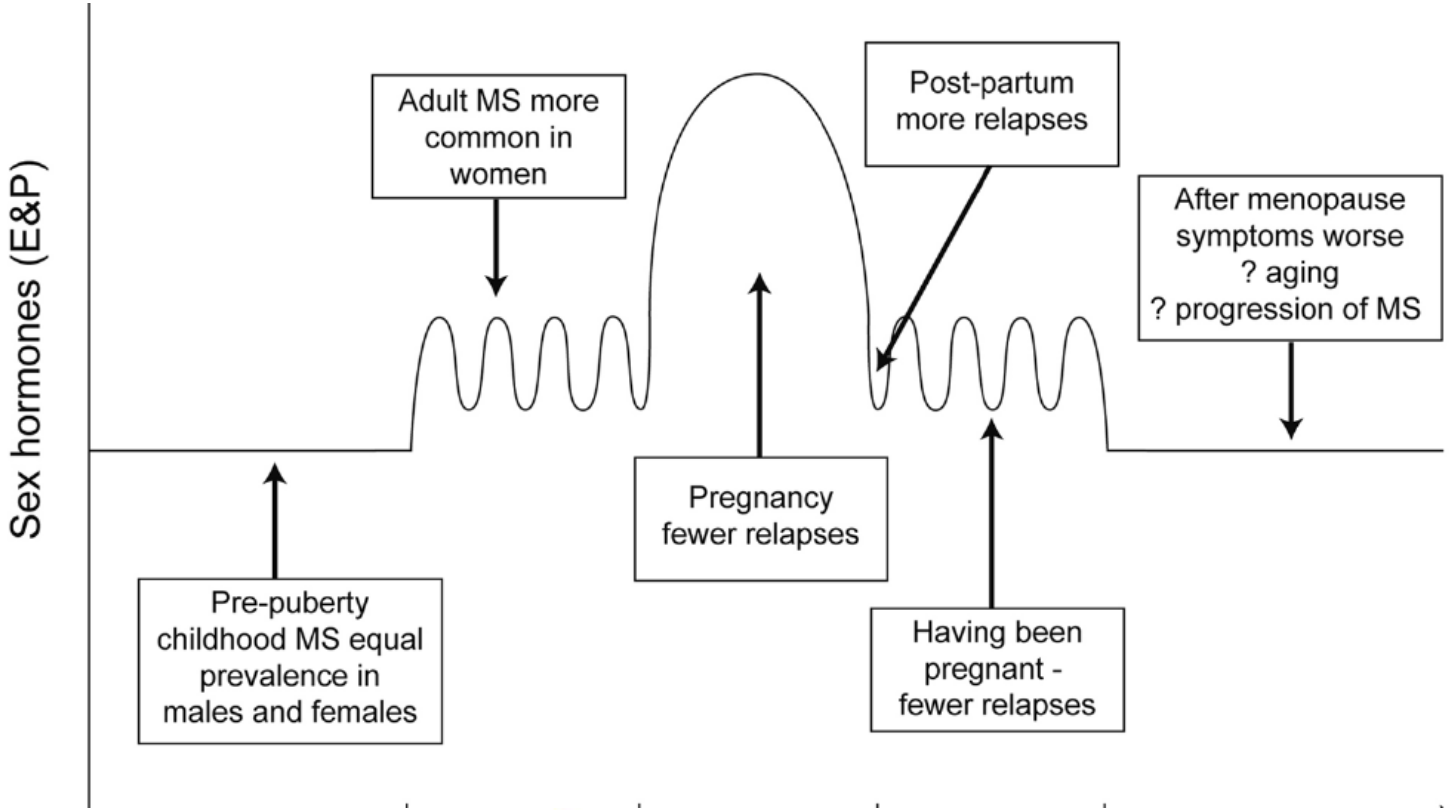
# MS & Female Reproductive Cycle



# Evolution of Sex Ratio in MS:

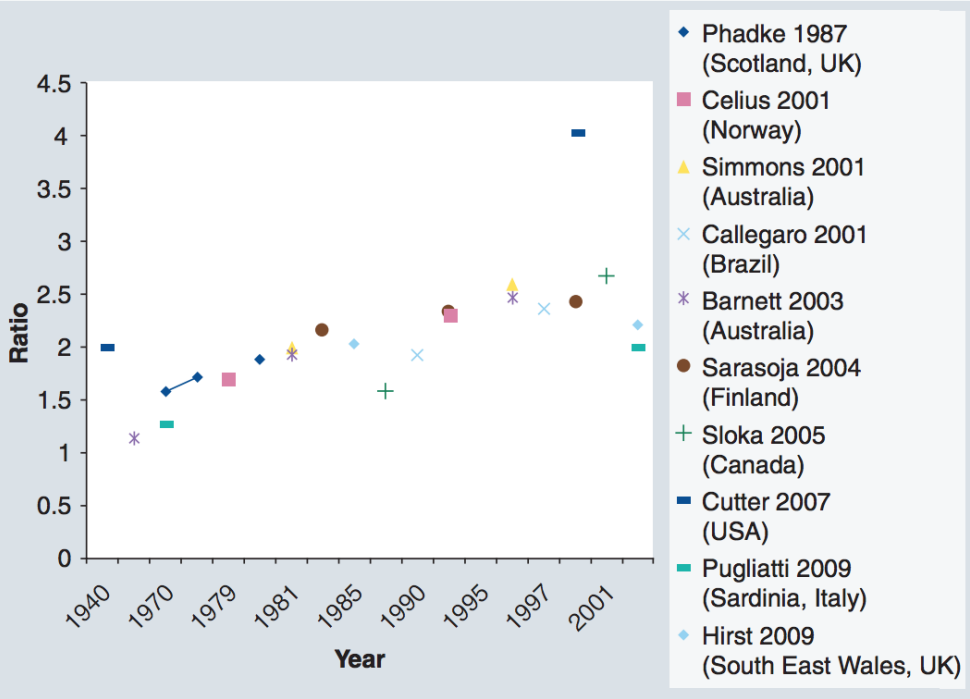



**Figure 1. Evolution of women:men MS ratio over time.**
Adapted from [9,10,12,13,21,23,33,34,37,39].

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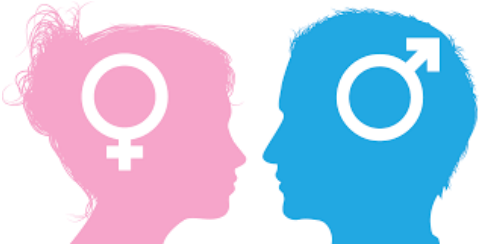
Jobin C. *et al.* Wom Health 2010.

# Differences in Onset/Course:



## Women:

- More frequently present with sensory symptoms
- Risk factor for more favorable course
- Mean age of onset is slightly earlier (F: age 32, M: 33.5)

## Men:

- More frequently present with cerebellar or brainstem symptoms
- Risk factor for more aggressive course
- Cognitive decline is greater among men



Jobin C. *et al.* Wom Health 2010.
Coyle PK. Neurol Clin 2005.

# Male MS:

- 3x less likely to develop MS
- Recover more poorly from MS relapses
- Increased rates of brain atrophy, disability and cognitive impairment



Bove R. *et al.* Clin Immunol 2013.

# Role of Testosterone in MS Risk:

- Testosterone (T) induces shift from Th1 → Th2, ↑ IL-5, ↑ IL-10, ↓ IFNγ, ↓ TNFα
- Age-related decline in T may explain later onset of MS in males compared to females
- A potential neuroprotective role warrants further investigation
- Reduced T may be a risk factor for MS in males



Chitnis T. *et al.* Mult Scler 2018.
Liva SM *et al.* J Immunol 2001.

# Testosterone in MS:

- In a cohort of 96 males with early MS, 40% had T in 1% range of normal.
- Positive association between testicular hypofunction & subsequent MS with RR=4.62 (95%CI: 2.3-8.24, p <0.00001)
- Low T has been associated with increased disability (EDSS) & cognitive decline (SDMT).
- Pilot study in 10 males with MS (age <65) with T gel supplementation → well tolerated, improvement in cognitive performance (PASAT) and slowed brain atrophy.

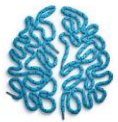


Bove R *et al.* Mult Scler 2014.
Pakpoor J. *et al*. Ann Neurol 2014.
Sicotte NL *et al.* Arch Neurol 2007.

# Risk of MS in Offspring:

| Relationship to Proband | Age adjusted risk estimate vs. General population |
|---|---|
| Parent | 2 - 3% |
| Sibling | 3 - 5%, can increase to 29.5% if 1 or both parents are affected. |
| **Offspring** | **2 – 3%** |

*Risk in general population with no FH ~ 0.2%



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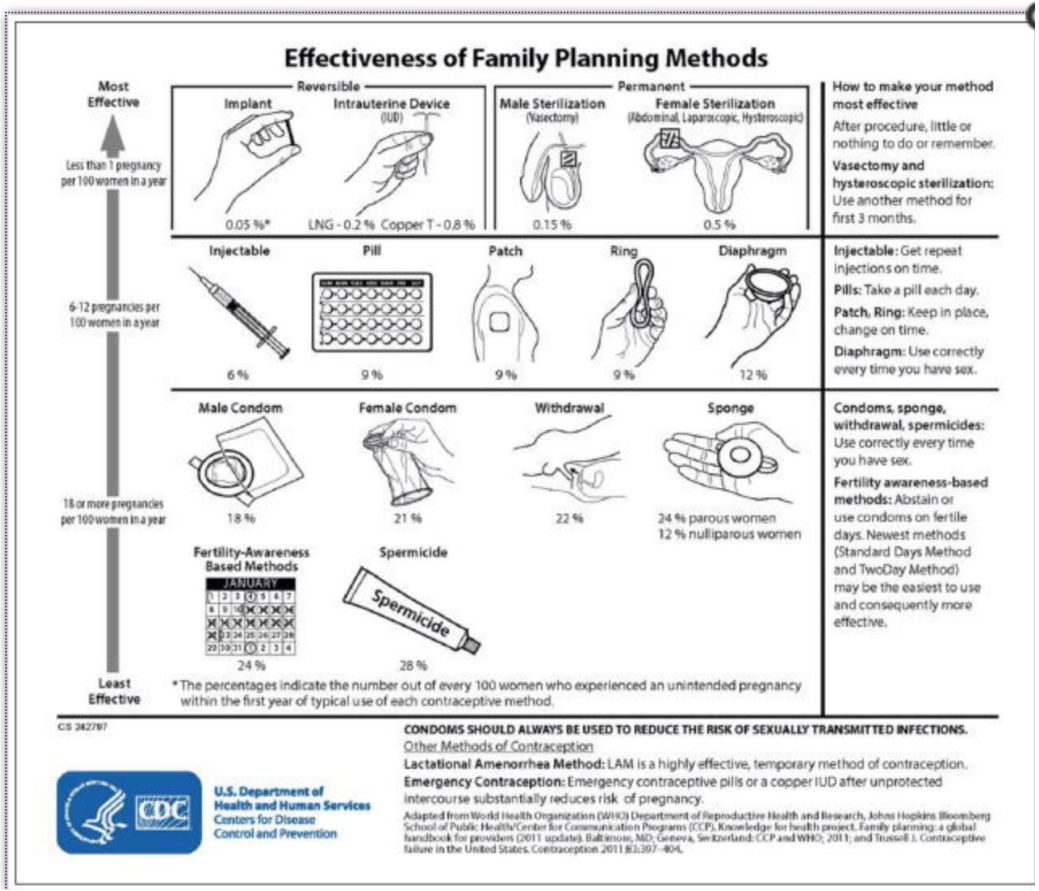
Sadovnick A.D. *Clin Genetics* 1999.

# MS & Contraception:




- Individualize
- Caution use of combined contraceptives in individuals with prolonged immobility ~ ↑ thromboembolic risk.
- DMT's do not alter effectiveness.
- Symptomatic medications (modafinil) can ↓ effectiveness.

Houtchens *et al.* Mult Scler 2017.

# Planning prior to Pregnancy:

- Pre-conception counseling for all women from initial diagnosis forward
- Individualized approach: consider need to minimize MS disease activity with consideration of maternal age, etc.
- DMT Specific approaches
- Contraception

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Krysko *et al*. 2020 Ther Adv Neurol Disord.

# MS Females have fewer children…

- Older DMTs did impact fertility: mitoxantrone, cyclophosphamide
- 12% of women in general population with infertility, may utilize Assisted Reproductive Technology
- Further studies needed, but ART may increase disease activity

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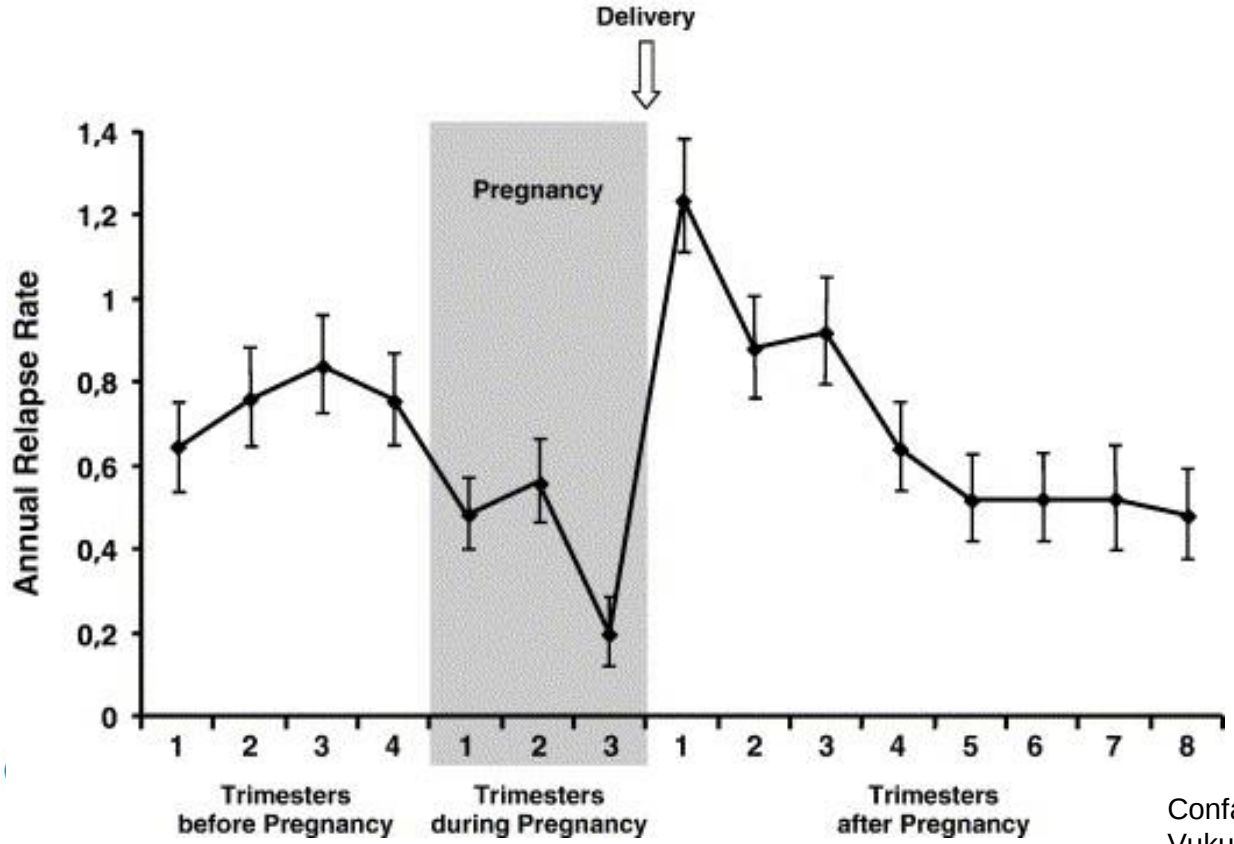
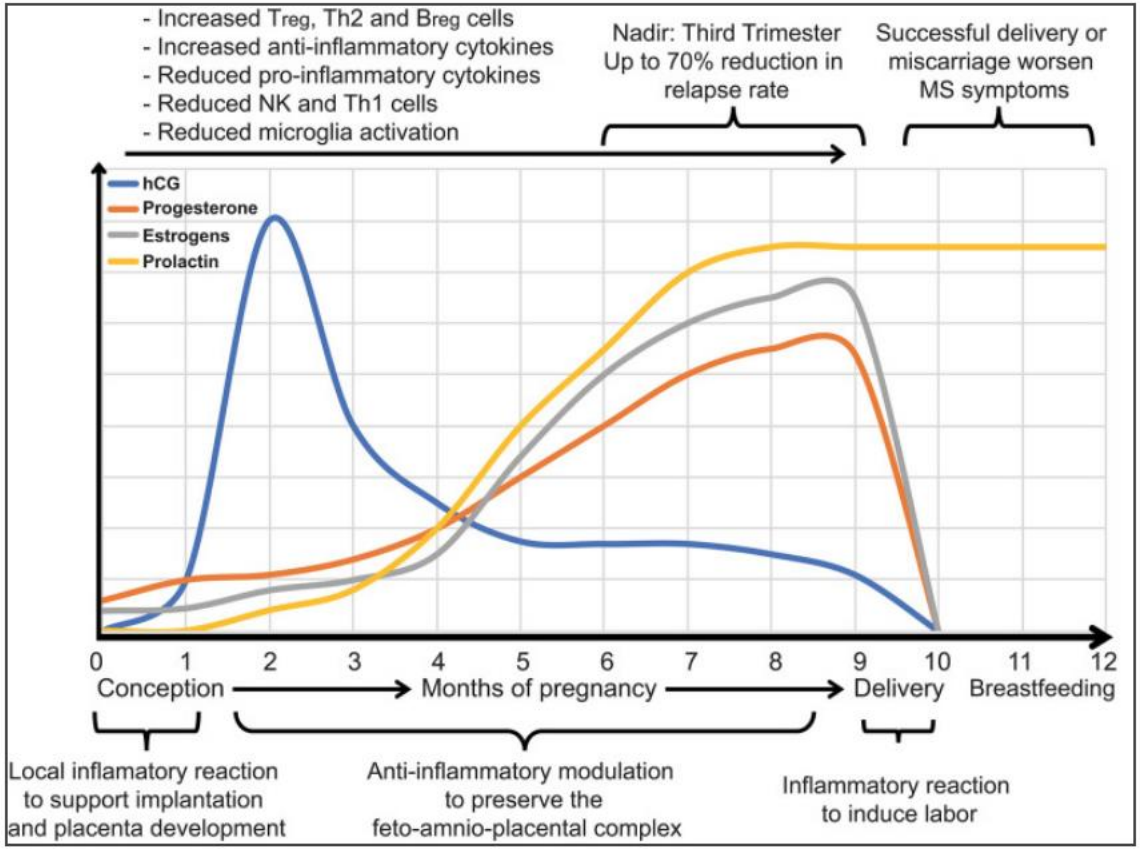
McCombe *et al.* Mult Scler 2015.

# MS Relapses & Pregnancy:




Confavreux C, *et al. N Engl J Med.* 1998.
Vukusic *et al. Brain* 2004.

# Immunology of Pregnancy:





Gilli F. et al. Front Neurol 2020.
Tafuri et al. *Science* 1995.
Garay et al. *J Steroid Biochem Mol Biol* 2007.
Zhang et al. *J Neurol Sci* 2003.
Saito et al. *Am J Reprod Immunol* 2010.

# Predictors of Post-partum Relapse:

**Table 3** *Indicators of the occurrence of at least one relapse during the 3-month period after delivery*

| Explanatory variable | Odds ratio | 95% CI | *P* |
|---|---|---|---|
| No. of relapses in pre-pregnancy year | 1.94 | 1.35–2.80 | <0.0001 |
| No. of relapses during pregnancy | 1.87 | 1.12–3.13 | 0.02 |
| MS duration (years) | 1.11 | 1.03–1.20 | 0.01 |

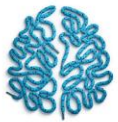
Multivariate logistic regression analysis among 223 women with multiple sclerosis. CI = confidence interval; MS = multiple sclerosis.



Vukusic *et al.* Brain 2004.

# Planning prior to Pregnancy: DMTs

- Injectables (GA, IFN) – use until conception, can consider continuing during pregnancy (discuss risk/benefit)
- Oral DMTs – do not continue in pregnancy, washout varies
- Cell depleting DMTs – before pregnancy & conception
- Special considerations for risk of disease reactivation upon discontinuation of DMT (ex: fingolimod, natalizumab) → consider transition to a cell depleting DMT before pregnancy
- NTZ may be continued during pregnancy every 8 weeks until 34 weeks gestation to prevent rebound/neonatal risks



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Krysko *et al*. 2020 Ther Adv Neurol Disord

# Planning prior to Pregnancy: MS Symptoms

- Pre-natal vitamins
- Vitamin D
- Smoking Avoidance
- Pelvic floor exercise
- Pre-emptive discussion on non-pharmacologic management of fatigue, insomnia, spasticity etc.
- Pro-actively address UTIs
- Coordinate care between neurology & MFM

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Mazor-Dray *et al.* 2009 J Mat Fet Neon Med
Krysko *et al.* 2020 Ther Adv Neurol Disord

# Assisted Reproductive Treatment & MS:

- Women with MS were more likely to use ART 4.9% vs. 0.9% (N=55,547)
- Evidence suggests that hormonal stimulation during ART increases relapse risk after unsuccessful stimulation
- Suggested mechanisms:
  - Majority off DMT before stimulation
  - Infertility may be a stressful life event
  - Immunological changes


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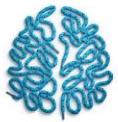
Jalkanen *et al. Mult Scler* 2010.
Hellwig K. *et al. Clin Immunol* 2013.

# During Pregnancy & Postpartum:

- If unintended pregnancy on unsuitable DMT, stop DMT, organ screening (accelerated elimination if teriflunomide).
- May consider stopping DMT during pregnancy (individualized)
- Schedule 3rd trimester visit to plan for post-partum
  - Most should be encouraged to breastfeed exclusively if able
  - Consider certain DMTs (injectable or monoclonal Ab) while breastfeeding
  - If not breastfeeding – resume DMT within 2-4 weeks post-partum



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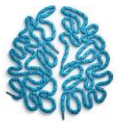
# Injectable DMT Safety:

| DMT | Animal data | First trimester exposure | Exposure throughout pregnancy | Recommendation* |
|---|---|---|---|---|
| **Injectables** | | | | |
| Glatiramer acetate[124] | No embryolethality or teratogenic effects seen[124] | No increased risk for SA or CA $n > 2500$[108–120] | Limited data shows no increased risk of adverse pregnancy outcomes in $n < 250$[110,113,115,116,120,121,123] | - Can be safely continued until positive pregnancy test<br>- Active approach: continue during pregnancy |
| Interferon-β[125–129] | Abortifacient effects seen at very high doses<br>No teratogenic effects or effects on fetal development[125–129] | No increased risk for SA or CA in $n = 1550$[108–110,113,115,118–120,122] | No increased risk of adverse pregnancy outcomes in $n < 100$[113,120–122] | - Can be safely continued until positive pregnancy test<br>- Active approach: continue during pregnancy |



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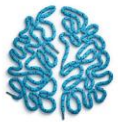
# Oral DMT Safety:

| | | | | |
|---|---|---|---|---|
| **Oral** | | | | |
| Dimethyl fumarate[130,131] | No embryolethality<br>No teratogenicity<br>At very high dose: low birth weight, delayed ossification and SA | Risk of SA and CA not elevated to date<br>*n* = 263, 214 known pregnancy outcomes<br>Risk of SA: 16/214 (7%)<br>Risk of CA: 7/214 (4%)<br>Hellwig ECTRIMS 2019[132] | Single cases, so risk unclear | - Stop with contraception or with positive pregnancy test<br>- In case of accidental exposure during pregnancy: stop<br>- EMA: may be used during pregnancy only if the potential benefit justifies potential risk to the fetus |
| Diroximel fumarate[133] | Embryolethality in one species (rabbit) and teratogenicity in one species (rabbit)<br>At very high dose: low birth weight, skeletal variation | Risk of SA and CA still unknown but likely similar to dimethyl fumarate | – | - Stop with contraception or with positive pregnancy test<br>- In case of accidental exposure during pregnancy: stop |
| Fingolimod[134,135] | Embryolethality in one species (rabbit) and teratogenicity in one species (rat) | 2-Fold increased risk of major congenital malformations (congenital heart disease, renal and musculoskeletal abnormalities) according to a registry<br>Registry with *n* = 113 live births with seven major malformations (6.2%)<br>Novartis safety database: 3.7% (25/678)<br>Pregnancy outcomes intensive monitoring (PRIM) program: 2% (8/393)<br>Hellwig ECTRIMS 2019[136]<br>**EMA alert in September 2019** | - | - EMA: contraindicated without effective contraception and during pregnancy<br>- FDA: use effective contraception and avoid pregnancy during and for 2 months after stopping<br>- Stop 2 months before conception and discuss bridging with another DMT<br>- In case of accidental exposure during pregnancy: stop and recommend organ screening ultrasound |
| Siponimod[137] | Embryolethality in one species (rabbit) and teratogenicity in one species (rat) | Risk of CA still unknown, but likely similar to fingolimod | – | - FDA: use effective contraception and avoid pregnancy during and for 10 days after stopping<br>- Stop 10 days before conception<br>- In case of accidental exposure during pregnancy: stop and recommend organ screening ultrasound |



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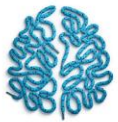
# Oral DMT Safety (2):

| | | | | |
|---|---|---|---|---|
| Cladribine[138,139] | Embryolethality in one species (mice) and teratogenicity in two species (rabbit and mice) | Risk of CA unknown, but report of 16 pregnancies within 6 months of cladribine (10 elective terminations; 3 healthy newborns; 2 SA; 1 ectopic) Galazka ECTRIMS 2017[140] | – | - Pregnancy safe 6 months after the last administration<br>- Risk of interaction between cladribine and oral contraception: women must also use mechanical contraception during the days of treatment and at least 4 weeks after the last dose |
| Teriflunomide[141,142] | Embryolethality and teratogenicity in two species (rabbit and rat) | No increased risk of CA<br>*n* = 437, 222 known pregnancy outcomes (risk of major malformation: 3.6% (1/28) in clinical trials, 0% (0/51) in post-marketing data)[143] | – | - FDA/EMA: contraindicated in pregnant women or women of reproductive potential not using effective contraception<br>- Stop before conception with accelerated elimination procedure (serum level < 0.02 mg/l twice, 2 weeks apart)<br>- In case of accidental exposure during pregnancy: stop, accelerated elimination procedure and recommend organ screening ultrasound |



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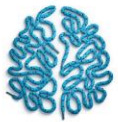
Krysko *et al*. 2020 *Ther Adv Neurol Disord*

# IV DMT Safety:

**Infusion**

| | | | | |
|---|---|---|---|---|
| Natalizumab[144,145] | No abortifacient or teratogenic effects, but immunological and hematologic effects[146] | Risk for SA and CA most likely not elevated[147]<br>*n* = 369, 355 known outcomes with 9.0% SA and 5.05% CA[148]<br>*n* = 92, 17.4% SA and 3.7% CA[147]<br>*n* = 98, 17.3% SA and 5.2% CA[149] | Hematologic abnormalities[150,151]<br>Possible increased risk of malformation (4/31) and anemia (5/31)[152] | - Case-by-case decision<br>- Consider switch to depleting agents<br>- Semi-active: stop with positive pregnancy test but risk of rebound relapse<br>- Active: maintain during pregnancy (can give every 8 weeks and last dose at approximately 34 weeks),[76] evaluate neonate for hematological abnormalities |
| Rituximab[153,154] | Transient peripheral B cell depletion[155] | Reduced B cell count in newborns[156,157] if treated during pregnancy<br>Risk for SA and CA likely not elevated<br>*n* = 102 with 12% SA and 4.5% CA or medical conditions[157] | Reduced B cell count in newborns[156,157] | - Attempt conception 1–3 months after the last dose[158]<br>- Discontinue in case of pregnancy<br>- Re-dose if not pregnant after 6–9 months<br>- Pregnancy test before each infusion |
| Ocrelizumab[159,160] | B cell depletion observed<br>In monkeys, increased perinatal mortality, renal, bone marrow and testicular toxicity[159,160] | Risk for SA likely not elevated<br>*n* = 118, 54 known outcomes with 7.4% (4/54) SA and 3% (1/32 at risk) stillbirth[161,162] | Limited[161,162] | - Attempt conception 1–3 months after the last dose<br>- Discontinue in case of pregnancy<br>- Re-dose if not pregnant after 6–9 months<br>- Pregnancy test before each infusion |
| Alemtuzumab[163,164] | Embryolethal when administered during organogenesis[163,164] and decreased B and T lymphocyte populations | Slightly elevated risk for SA cannot be excluded<br>*n* = 193, 167 known outcomes with 22% SA, 0% CA, 0.6% stillbirth[165] | – | - Conception 4 months after last infusion may be attempted<br>- Pregnancy test prior to each course<br>- Monitor thyroid function and antithyroid antibodies (placental transfer of anti-thyrotropin receptor antibodies resulting in neonatal Graves' disease observed)[163] |



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# Relapse Management in Pregnancy:

- **Steroids:**
  - Try to avoid in 1st trimester
  - Probably safe in the 2nd/3rd trimester
  - Crosses the placenta
  - May ↑ risk of cleft palate in 1st trimester or cause low birth weight
  - Methylprednisolone, prednisone preferred (< 10% reaches fetus) vs. dexamethasone (full maternal dose reaches fetus)
- **IVIG**: Probably safe, no effects on fetal immune system

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Gur C *et al.* Reprod Tox 2004.
Park-Wyllie L. *et al.* Teratology 2000.

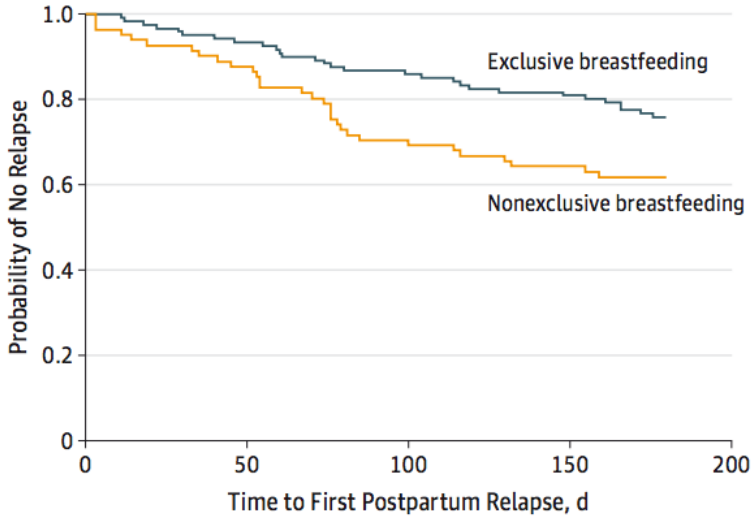
# Postpartum Considerations:

# Breastfeeding & MS:

- Does not increase risk of relapse.
- **Exclusive Breastfeeding (BF) may reduce relapses post-partum**.
- Decision to breastfeed and timing of resuming DMT for MS based on consensus between mother and physician.

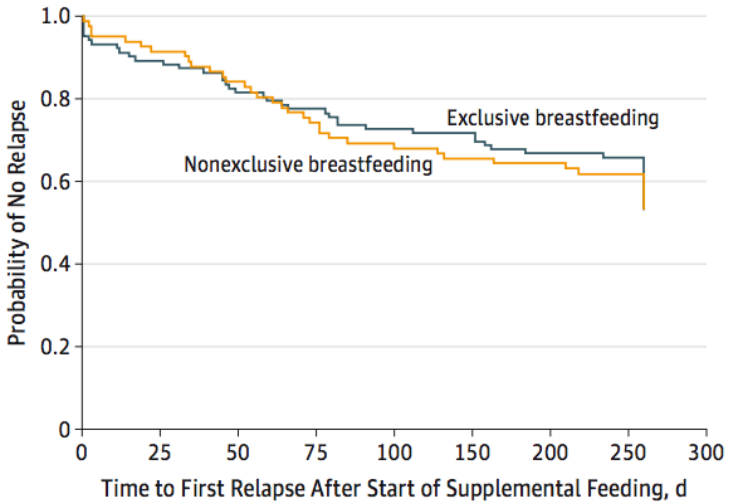
# Breastfeeding & MS:

**Figure 1. Exclusive Breastfeeding and the Risk of Postpartum Multiple Sclerosis Relapse**




| No. at risk | | | | | |
|---|---|---|---|---|---|
| Breastfeeding | | | | | |
| Exclusive | 120 | 112 | 103 | 97 | 91 |
| Nonexclusive | 81 | 71 | 57 | 52 | 50 |

**Figure 2. Multiple Sclerosis Relapse After Introduction of Supplemental Feeding Among Women Who Breastfed Exclusively and Those Who Did Not**



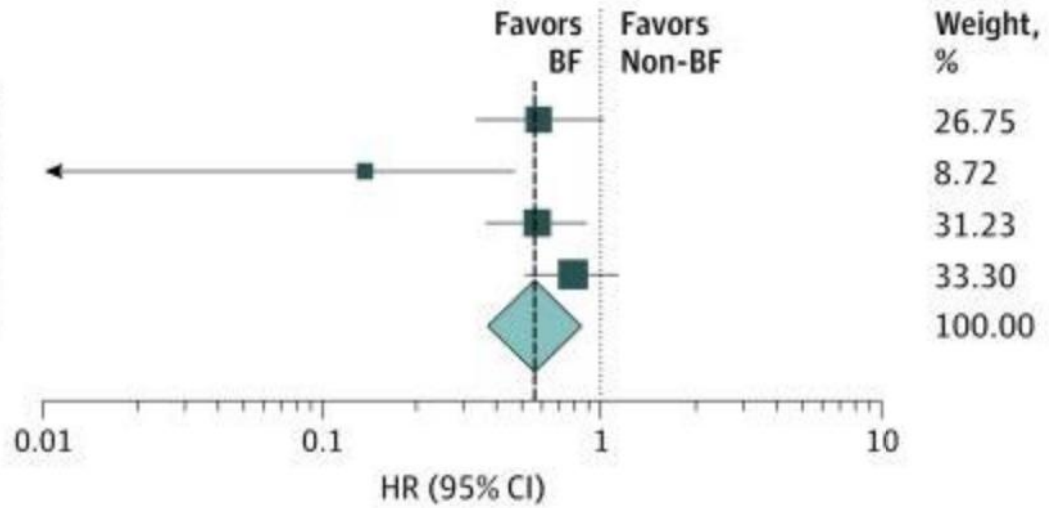

| No. at risk | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Breastfeeding | | | | | | | | | |
| Exclusive | 120 | 91 | 83 | 79 | 74 | 68 | 67 | 64 | 61 |
| Nonexclusive | 81 | 74 | 68 | 60 | 55 | 52 | 49 | 46 | 45 |

Hellwig et al. JAMA Neurol 2015.

# BF & Post-partum Relapse:

| Source | HR (95% CI) |
|---|---|
| Hellwig et al,[10] 2015 | 0.59 (0.35-0.98) |
| Langer-Gould et al,[31] 2009 | 0.14 (0.04-0.48) |
| Langer-Gould et al,[12] 2019 | 0.58 (0.38-0.88) |
| Portaccio et al,[8] 2014 | 0.78 (0.53-1.13) |
| Overall $I^2 = 57.5\%$; $P = .07$ | 0.57 (0.38-0.85) |

Weights are from random-effects analysis.

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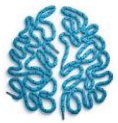
Krysko *et al.* JAMA Neurol 2020.

# Postpartum Relapse Predictors:

| Protective against postpartum relapse | Risk factors associated with postpartum relapse | No consistent effect on postpartum relapse |
|---|---|---|
| - Pre-conception disease modifying therapy use<br>- Lower disease activity pre-conception<br>- Early re-initiation of disease modifying therapy<br>- Potentially breastfeeding, particularly exclusive | - Higher disease activity pre-conception (preceding 12 months)<br>- Higher disease activity during pregnancy<br>- Higher disability level at onset of pregnancy<br>- Longer wash out period after discontinuation of high-efficacy disease-modifying therapy | - Age (neither at the onset of MS or pregnancy)<br>- Number of prior pregnancies<br>- Infant sex<br>- Cesarean section<br>- Use of epidural anesthesia<br>- Postpartum use of IVIG or IV steroids |

IV, intravenous; IVIG, intravenous immune globulin; MS, multiple sclerosis.



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Krysko *et al.* 2020 Ther Adv Neurol Disord

# Post-partum Depression

- PPD: 7-19% all women postpartum
- Screen with Edinburgh Postnatal Depression Scale
- PPD is under-explored in MS

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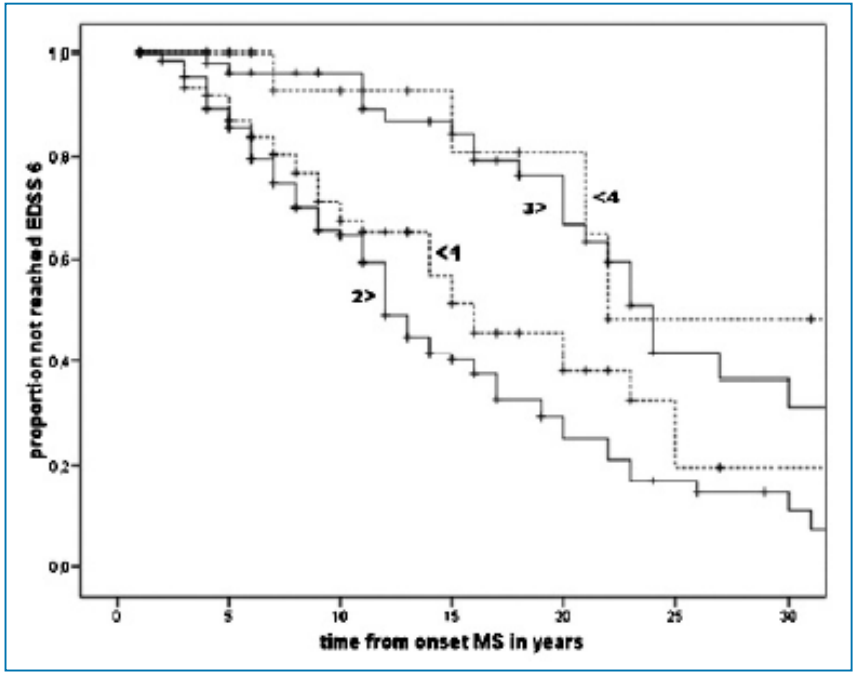
Razaz *et al. Mult Scler 2016.*

# Long Term Effects of Pregnancy on MS




**Time to EDSS = 6:**

1: No children

2: Pregnancy prior to MS onset

**3: Pregnancy after MS onset**

**4: Pregnancy before & after MS onset**

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D'hoogue MB *et al. J Neurol Neurosurg Psy* 2010.

# Post-partum MS Care:

- Fatigue → sleep disruption, hormonal changes, mood
- Strengh, Balance, Gait → PT, exercise
- Bladder & Bowel → pelvic floor therapy
- Endocrine changes: thyroid, Vitamin D
- MRI monitoring, Re-initiation of MS DMT

# Parenting & MS:

- Parent(s) can:
  - Involve available support system (friends, family, etc.)
  - Consider financial resources
  - Consider personal and family priorities
  - Create an open conversation with children:
    - Age-specific information
    - Newsletter for Kids “Keep Smyelin” via NMSS
    - Camp Connect via NMSS

# MS: Menopause & Beyond:

# Menopause & MS:

- **Hot flashes can exacerbate MS symptoms (heat sensitivity)**
- Some patients report worsening of fatigue & bladder symptoms
- Declines in AMH were associated with clinically and statistically significant increases in disability, gray matter atrophy (adjusted for age, BMI & disease duration) in 10 year longitudinal cohort.

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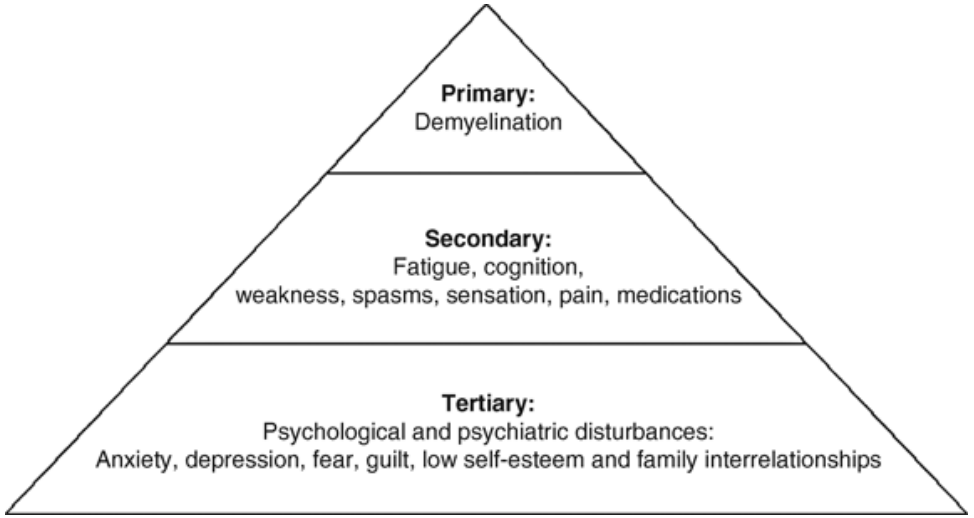
Graves *et al. Neurology 2018*.

# Sexual dysfunction in MS:

## Common in MS:

- 50-80% of Women
- 50-90% of Men
- Most underreported & under-treated symptom

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Gromisch ES et al. *Int J MS Care.* 2016.

# SD Management in MS:

- ASK!
- Maximize MS DMT
- Address symptoms (bladder, fatigue, spasticity, etc.)
- Minimize contributing medications
- Lubrication, Vibrators
- Male Erectile Dysfunction: sildenafil, vardenifil
- Females: flibanserin, Eros device
- Referral to Urology, Gynecology, Couples Counseling


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Domingo et al. *Int J MS Care.* 2018.
Namey M. *Int J MS Care.* 2012;14 Suppl 1.

# Conclusions:

- MS has a 3:1 predominance in women vs. men
- Sex Homones impact the immune system and MS course
- Low Testosterone may serve as a risk factor for MS in males
- More studies are needed to determine the benefits and risks of Testosterone in Men with MS

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# Conclusions:

- Patients with MS should be counseled early and often on reproduction, pregnancy planning and DMT safety
- Care of females with MS is individualized based on disease activity, lifestyle and plans for family
- Pregnancy in MS is not high risk
- Pregnancy is protective against MS disease activity with an increased relapse risk in the “4$^{th}$ trimester
- Exclusive breastfeeding may be protective in MS
- MS often worsens in menopause & beyond, further research needed to understand

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# Questions?

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# OhioHealth MULTIPLE SCLEROSIS


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