



Gender Differences in Multiple Sclerosis

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Disclosures

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Outline

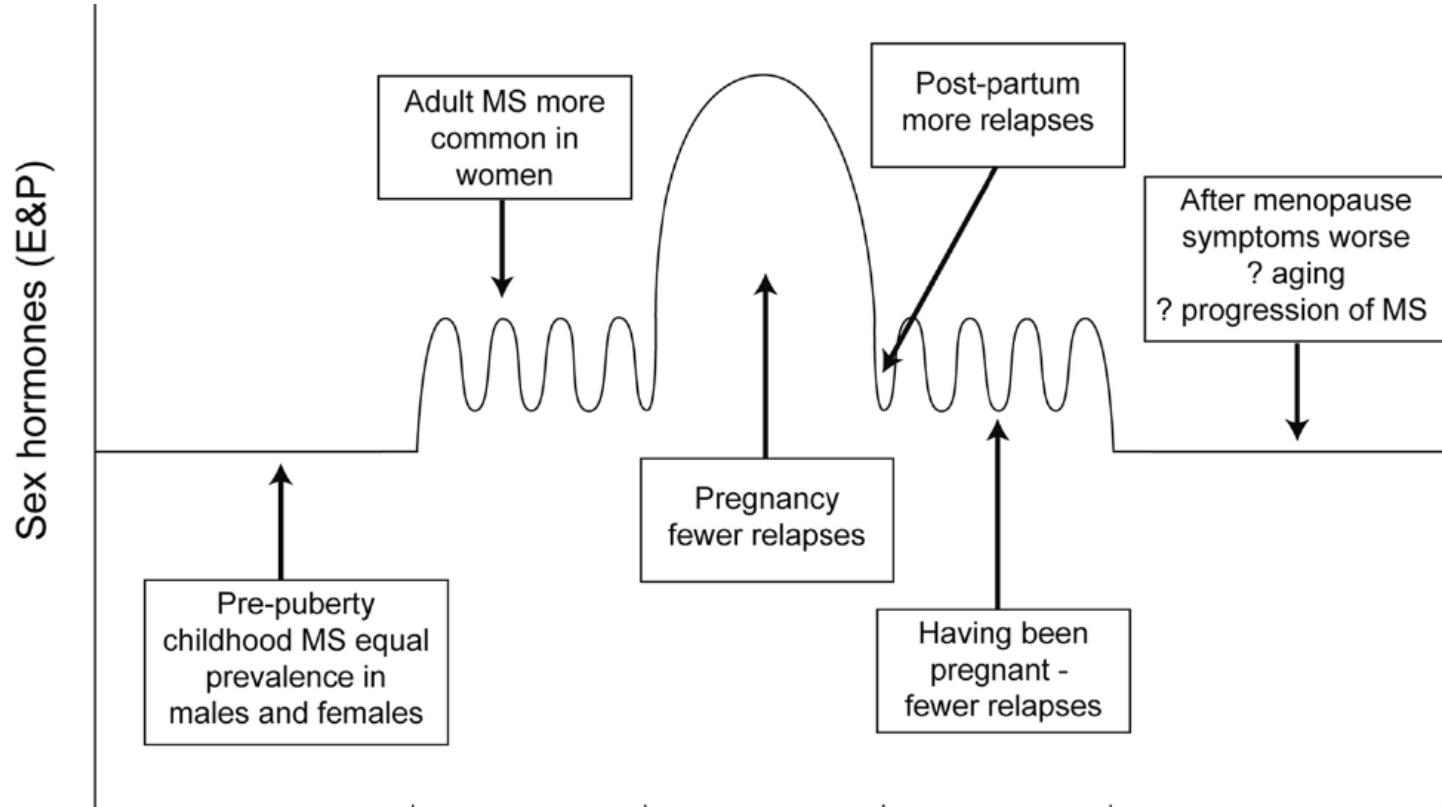
- Impact of sex on MS susceptibility
- Testosterone impact on MS
- Impact of pregnancy on MS disease activity
- MS management strategies: pre-pregnancy, pregnancy & post-partum
- Reproductive aging in MS
- Sexual dysfunction in MS



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MS & Female Reproductive Cycle



Evolution of Sex Ratio in MS:

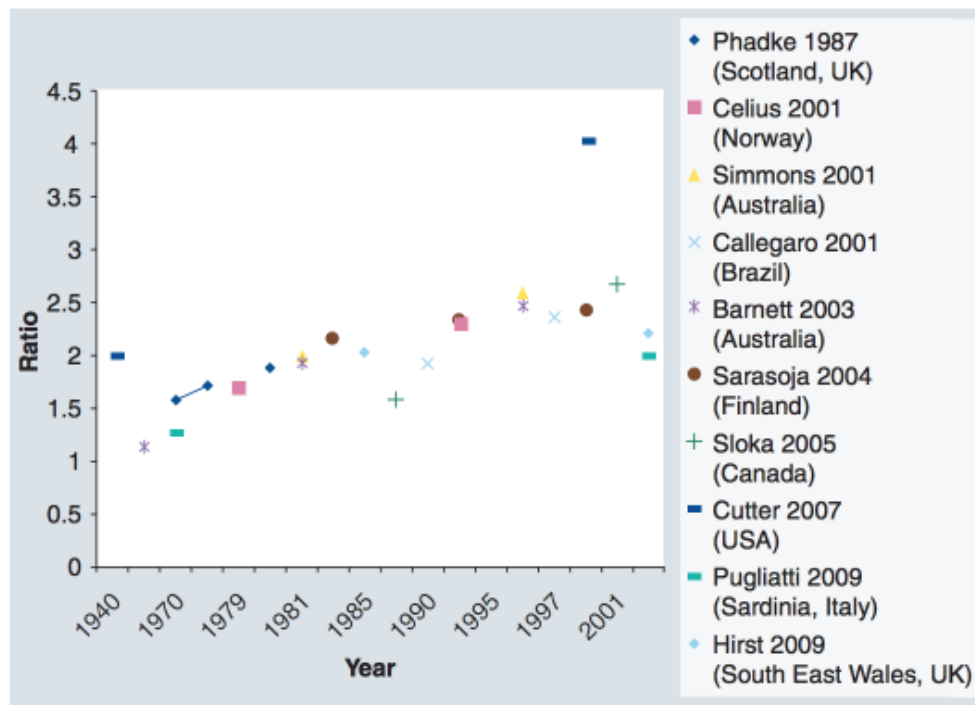


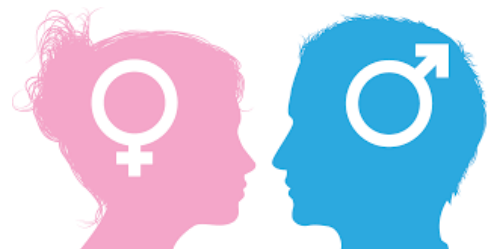
Figure 1. Evolution of women:men MS ratio over time.

Adapted from [9,10,12,13,21,23,33,34,37,39].



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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



Male MS:

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



Role of Testosterone in MS Risk:

- Testosterone (T) induces shift from Th1 → Th2, ↑ IL-5, ↑ IL-10, ↓ IFN γ , ↓ TNF α
- 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



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.



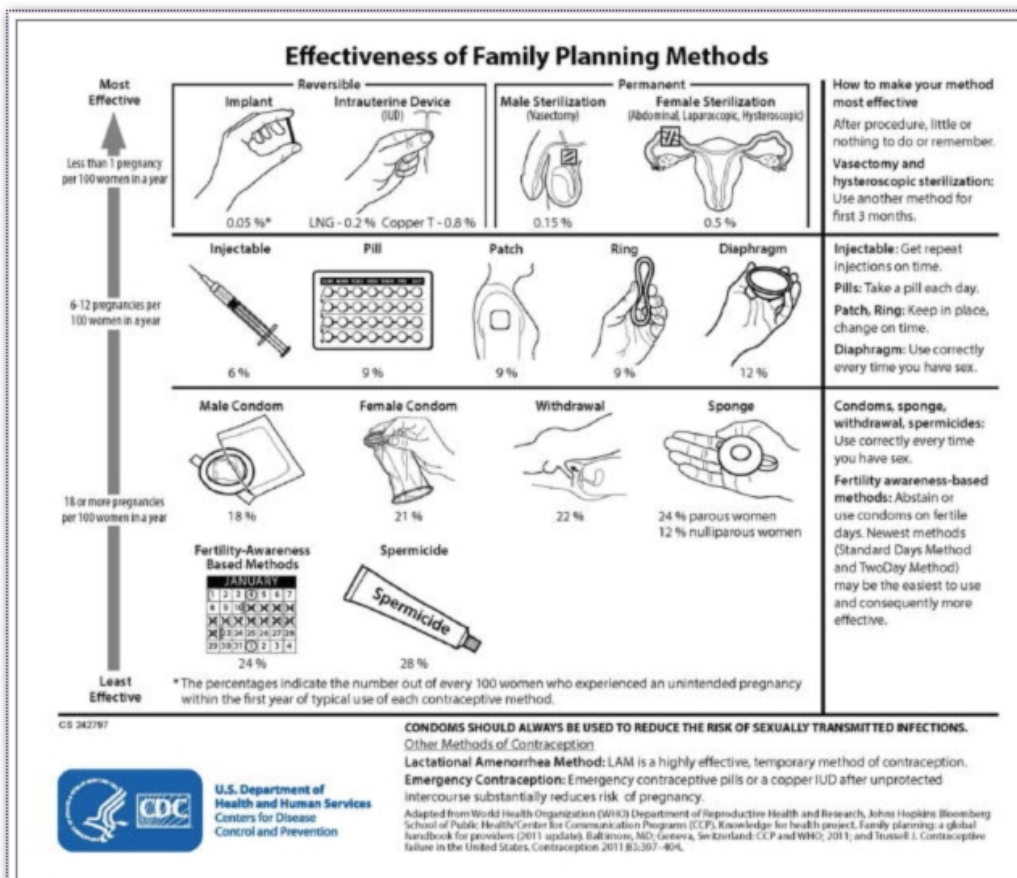
Risk of MS in Offspring:

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%



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.

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

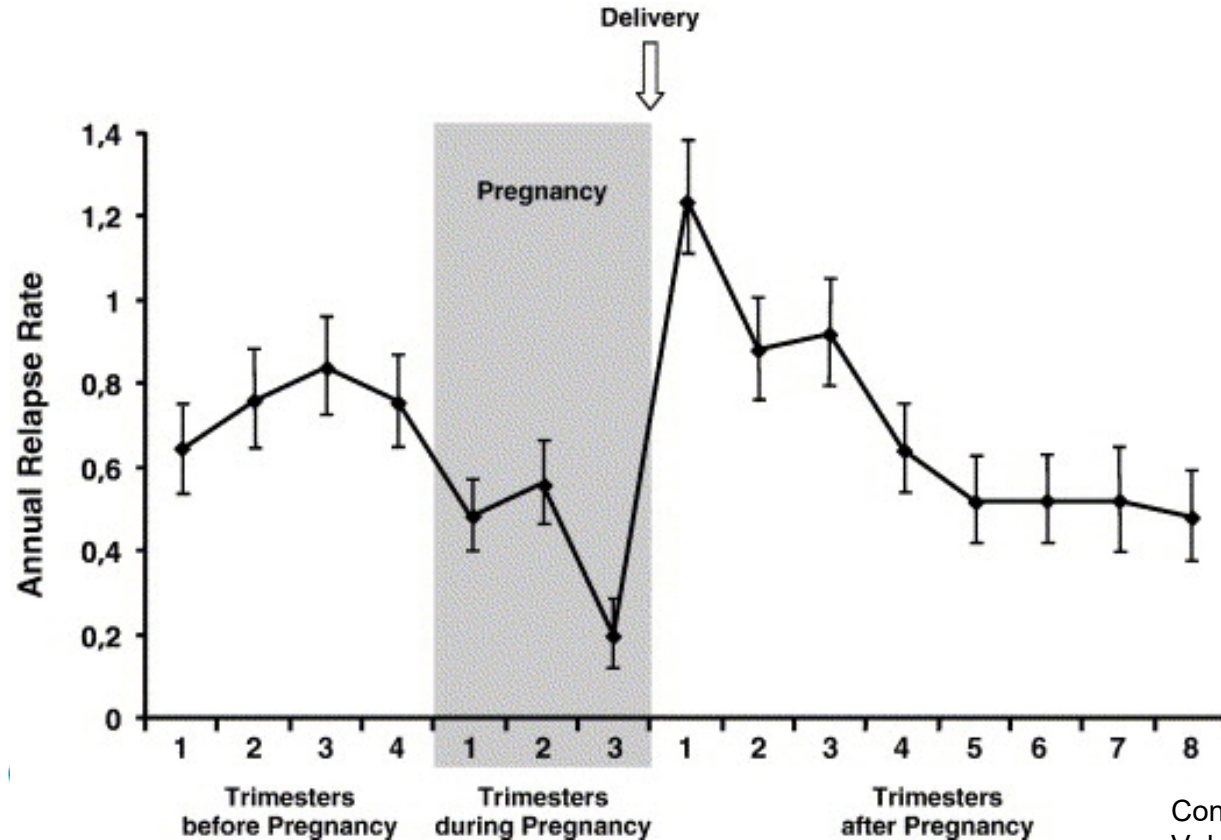


MS Females have fewer children...

- 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

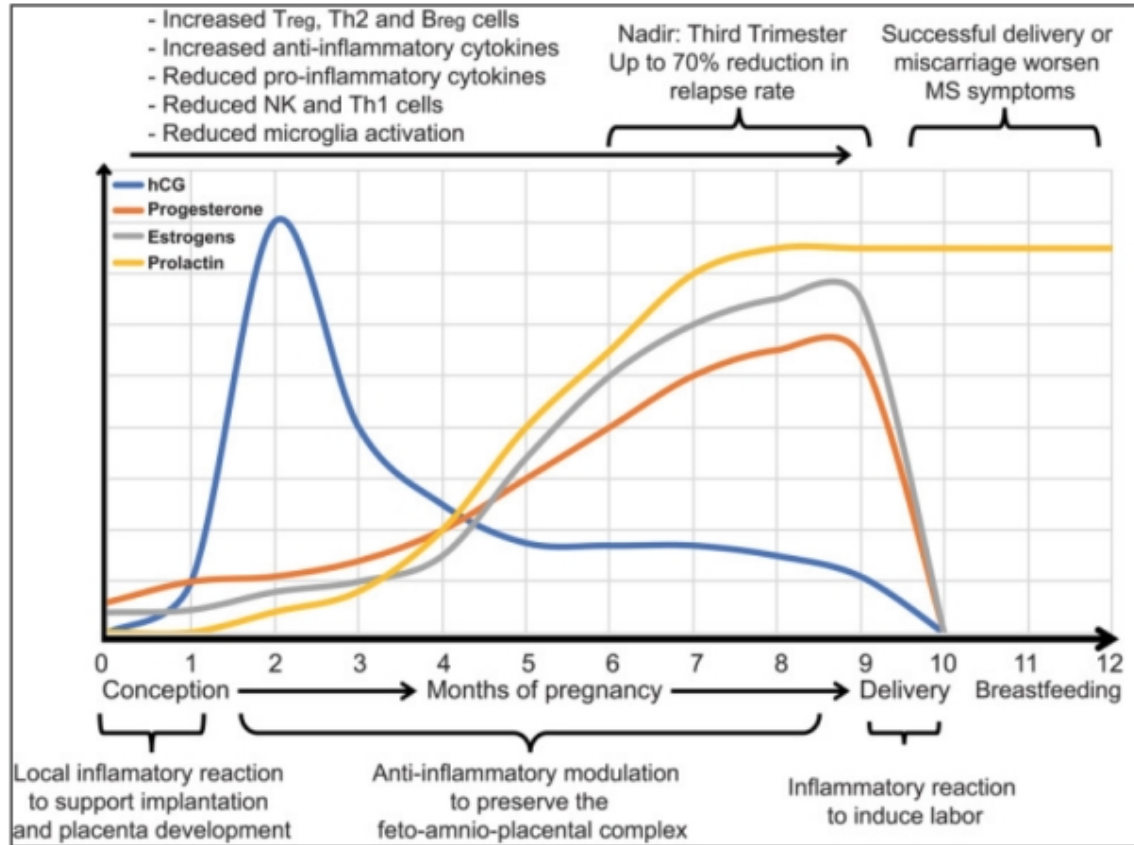


MS Relapses & Pregnancy:



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

Immunology of Pregnancy:



Gilli F. et al. *Front Neurol* 2020.
Tafari 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	<i>P</i>
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.



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



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



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



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



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 in $n > 2500$ ¹⁰⁸⁻¹²⁰	Limited data shows no increased risk of adverse pregnancy outcomes in $n < 250$ ^{110,113,115,116,120,121,123}	<ul style="list-style-type: none"> - Can be safely continued until positive pregnancy test - Active approach: continue during pregnancy
Interferon- β ¹²⁵⁻¹²⁹	Abortifacient effects seen at very high doses 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}	<ul style="list-style-type: none"> - Can be safely continued until positive pregnancy test - Active approach: continue during pregnancy



Oral DMT Safety:

Oral				
Dimethyl fumarate ^{130,131}	No embryoletality No teratogenicity At very high dose: low birth weight, delayed ossification and SA	Risk of SA and CA not elevated to date $n=263, 214$ known pregnancy outcomes Risk of SA: 16/214 (7%) Risk of CA: 7/214 (4%) Hellwig ECTRIMS 2019 ¹³²	Single cases, so risk unclear	<ul style="list-style-type: none"> - Stop with contraception or with positive pregnancy test - In case of accidental exposure during pregnancy: stop - EMA: may be used during pregnancy only if the potential benefit justifies potential risk to the fetus
Diroximel fumarate ¹³³	Embryoletality in one species (rabbit) and teratogenicity in one species (rabbit) At very high dose: low birth weight, skeletal variation	Risk of SA and CA still unknown but likely similar to dimethyl fumarate	-	<ul style="list-style-type: none"> - Stop with contraception or with positive pregnancy test - In case of accidental exposure during pregnancy: stop
Fingolimod ^{134,135}	Embryoletality 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 Registry with $n=113$ live births with seven major malformations (6.2%) Novartis safety database: 3.7% (25/678) Pregnancy outcomes intensive monitoring (PRIM) program: 2% (8/393) Hellwig ECTRIMS 2019 ¹³⁶ EMA alert in September 2019	-	<ul style="list-style-type: none"> - EMA: contraindicated without effective contraception and during pregnancy - FDA: use effective contraception and avoid pregnancy during and for 2 months after stopping - Stop 2 months before conception and discuss bridging with another DMT - In case of accidental exposure during pregnancy: stop and recommend organ screening ultrasound
Siponimod ¹³⁷	Embryoletality in one species (rabbit) and teratogenicity in one species (rat)	Risk of CA still unknown, but likely similar to fingolimod	-	<ul style="list-style-type: none"> - FDA: use effective contraception and avoid pregnancy during and for 10 days after stopping - Stop 10 days before conception - In case of accidental exposure during pregnancy: stop and recommend organ screening ultrasound



Oral DMT Safety (2):

Cladribine^{138,139}

Embryoletality 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 2017¹⁴⁰

-

- Pregnancy safe 6 months after the last administration
- 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}

Embryoletality and teratogenicity in two species (rabbit and rat)

No increased risk of CA
 $n = 437$, 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
- Stop before conception with accelerated elimination procedure (serum level <0.02 mg/l twice, 2 weeks apart)
- In case of accidental exposure during pregnancy: stop, accelerated elimination procedure and recommend organ screening ultrasound



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IV DMT Safety:

Infusion

Natalizumab ^{144,145}	No abortifacient or teratogenic effects, but immunological and hematologic effects ¹⁴⁴	Risk for SA and CA most likely not elevated ¹⁴⁷ $n = 369$, 355 known outcomes with 9.0% SA and 5.05% CA ¹⁴⁸ $n = 92$, 17.4% SA and 3.7% CA ¹⁴⁷ $n = 98$, 17.3% SA and 5.2% CA ¹⁴⁹	Hematologic abnormalities ^{150,151} Possible increased risk of malformation [4/31] and anemia [5/31] ¹⁵²	<ul style="list-style-type: none"> - Case-by-case decision - Consider switch to depleting agents - Semi-active: stop with positive pregnancy test but risk of rebound relapse - 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 Risk for SA and CA likely not elevated $n = 102$ with 12% SA and 4.5% CA or medical conditions ¹⁵⁷	Reduced B cell count in newborns ^{156,157}	<ul style="list-style-type: none"> - Attempt conception 1–3 months after the last dose¹⁵⁸ - Discontinue in case of pregnancy - Re-dose if not pregnant after 6–9 months - Pregnancy test before each infusion
Ocrelizumab ^{159,160}	B cell depletion observed in monkeys, increased perinatal mortality, renal, bone marrow and testicular toxicity ^{159,160}	Risk for SA likely not elevated $n = 118$, 54 known outcomes with 7.4% (4/54) SA and 3% (1/32 at risk) stillbirth ^{161,162}	Limited ^{161,162}	<ul style="list-style-type: none"> - Attempt conception 1–3 months after the last dose - Discontinue in case of pregnancy - Re-dose if not pregnant after 6–9 months - 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 $n = 193$, 167 known outcomes with 22% SA, 0% CA, 0.6% stillbirth ¹⁶⁵	-	<ul style="list-style-type: none"> - Conception 4 months after last infusion may be attempted - Pregnancy test prior to each course - Monitor thyroid function and antithyroid antibodies (placental transfer of anti-thyrotropin receptor antibodies resulting in neonatal Graves' disease observed)¹⁶³



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





Postpartum Considerations:

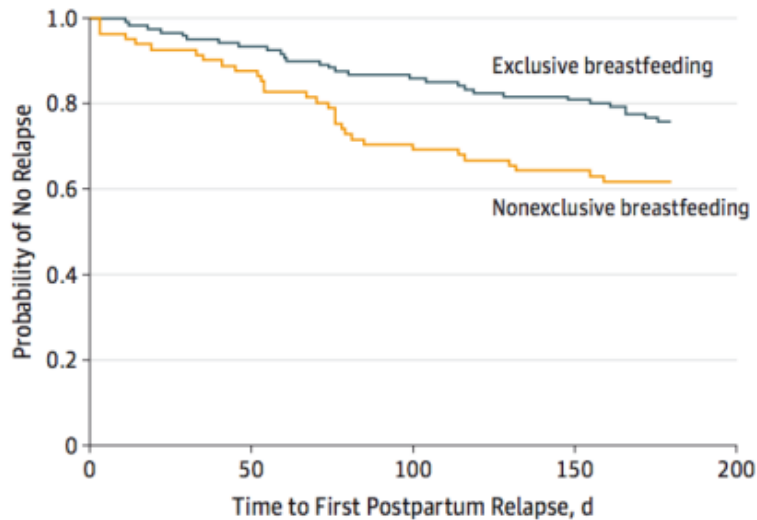
Breastfeeding & MS:

- 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.



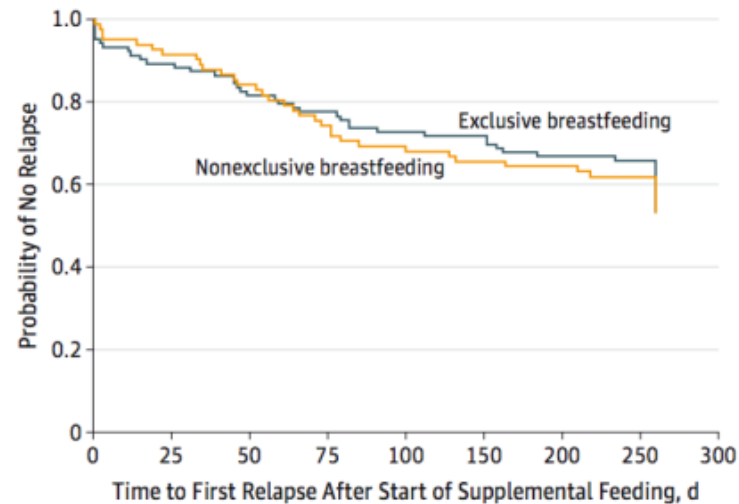
Breastfeeding & MS:

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



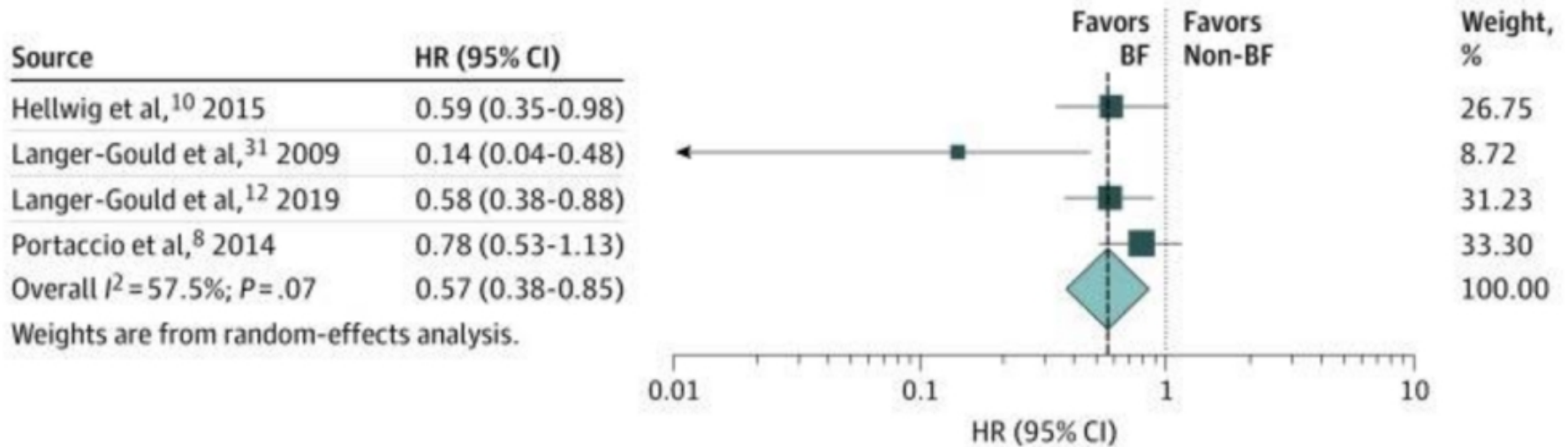
No. at risk						
Breastfeeding						
Exclusive	120	112	103	97	91	50
Nonexclusive	81	71	57	52	50	50

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		

BF & Post-partum Relapse:



Postpartum Relapse Predictors:

Protective against postpartum relapse	Risk factors associated with postpartum relapse	No consistent effect on postpartum relapse
<ul style="list-style-type: none">- Pre-conception disease modifying therapy use- Lower disease activity pre-conception- Early re-initiation of disease modifying therapy- Potentially breastfeeding, particularly exclusive	<ul style="list-style-type: none">- Higher disease activity pre-conception (preceding 12 months)- Higher disease activity during pregnancy- Higher disability level at onset of pregnancy- Longer wash out period after discontinuation of high-efficacy disease-modifying therapy	<ul style="list-style-type: none">- Age (neither at the onset of MS or pregnancy)- Number of prior pregnancies- Infant sex- Cesarean section- Use of epidural anesthesia- Postpartum use of IVIG or IV steroids
IV, intravenous; IVIG, intravenous immune globulin; MS, multiple sclerosis.		

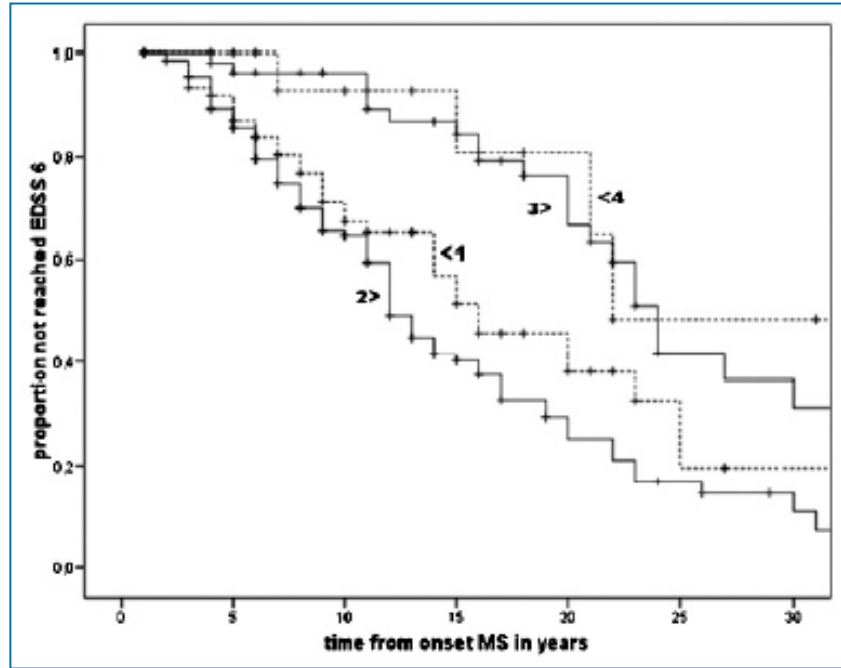


Post-partum Depression

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



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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Post-partum MS Care:

- Fatigue → sleep disruption, hormonal changes, mood
- Strength, 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:

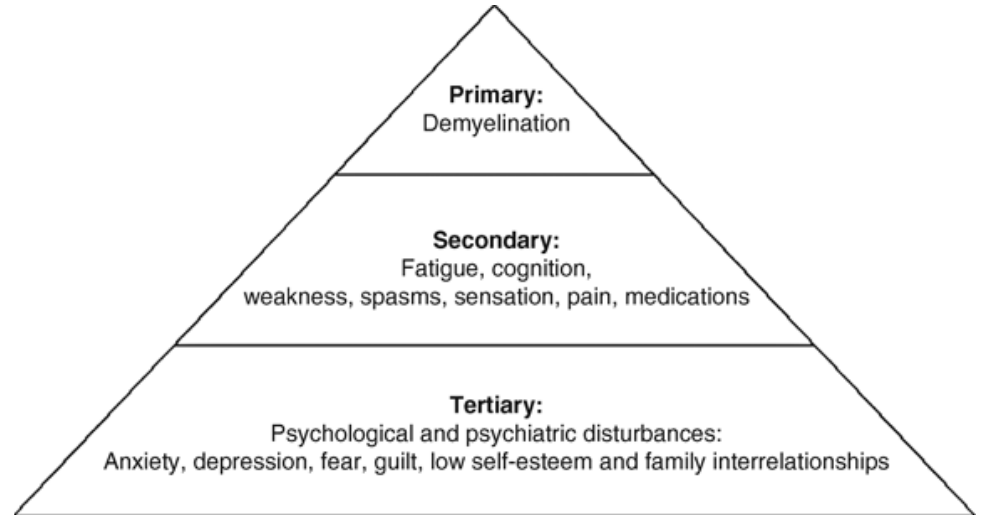
- **Hot flashes can exacerbate MS symptoms (heat sensitivity)**
- Some patients report worsening of fatigue & bladder symptoms
- Declines in AMH were associated with clinically and statistically significant increases in disability, gray matter atrophy (adjusted for age, BMI & disease duration) in 10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



Sexual dysfunction in MS:

Common in MS:

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



SD Management in MS:

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



**KEEP
CALM
AND
JUST
ASK**



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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 Hormones 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



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 “4th trimester
- Exclusive breastfeeding may be protective in MS
- MS often worsens in menopause & beyond, further research needed to understand



Questions?



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OhioHealth MULTIPLE SCLEROSIS



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