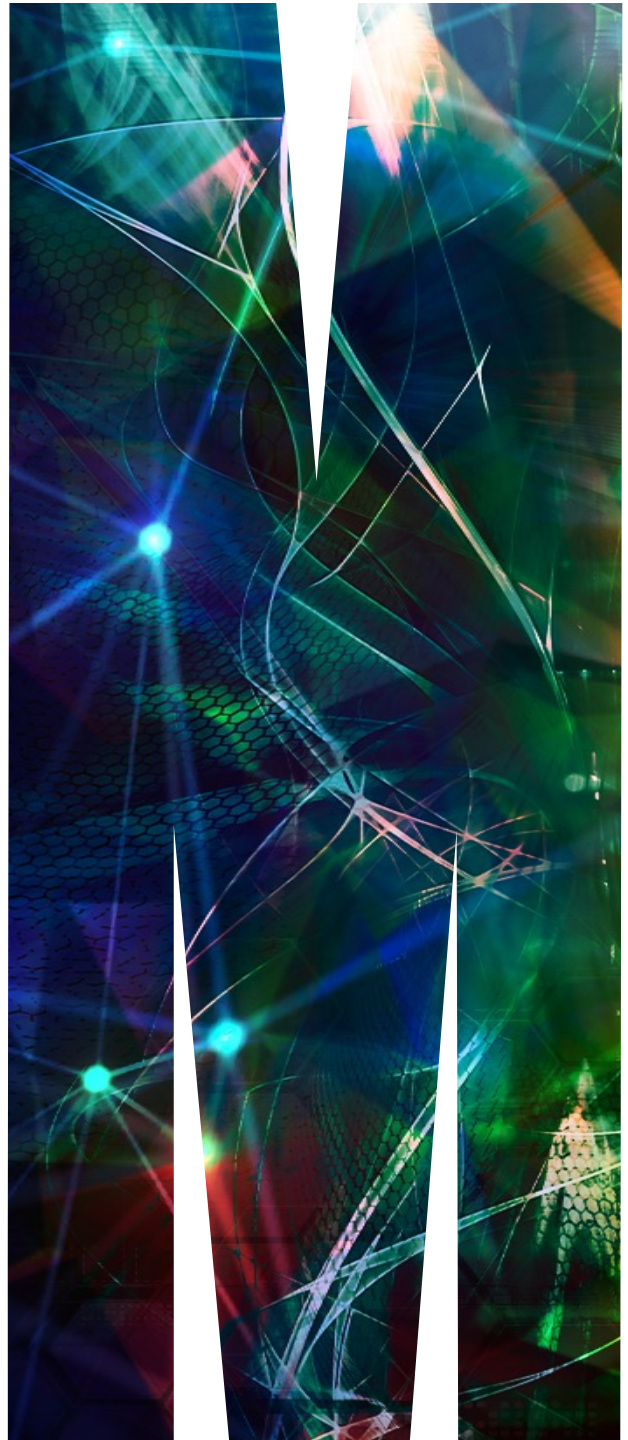
MONASH University

Fertility, Pregnancy and Multiple Sclerosis



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MSBase
Neuro-Immunology Registry

- Chair Scientific Leadership Group of MSBase
- Co-Chair and Scientific Lead of the MSBase Pregnancy, Neonatal Outcomes and Women's Health sub-committee

91,733 Participant Records from around the World

Patient information (sex, DOB, symptom onset date)

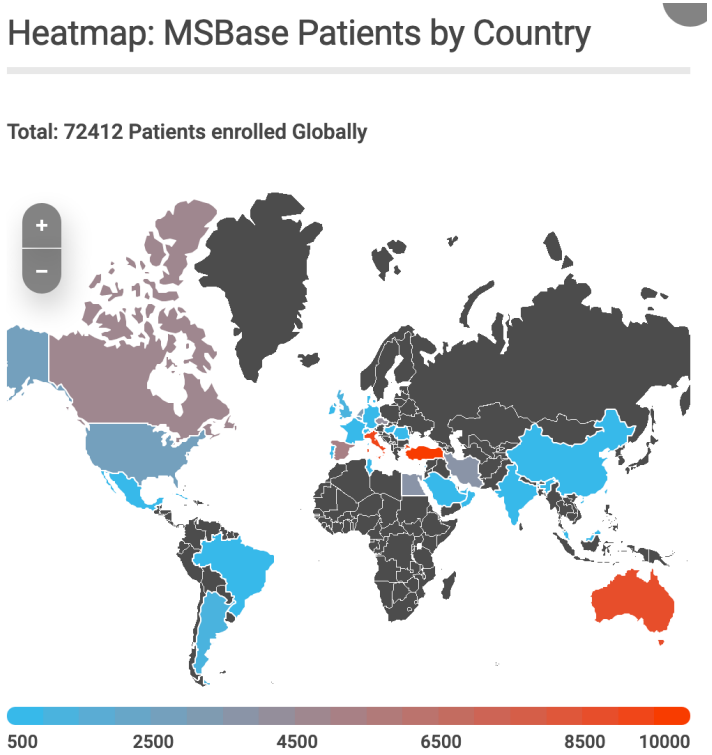
Disability measurements

Relapse information

Treatment information

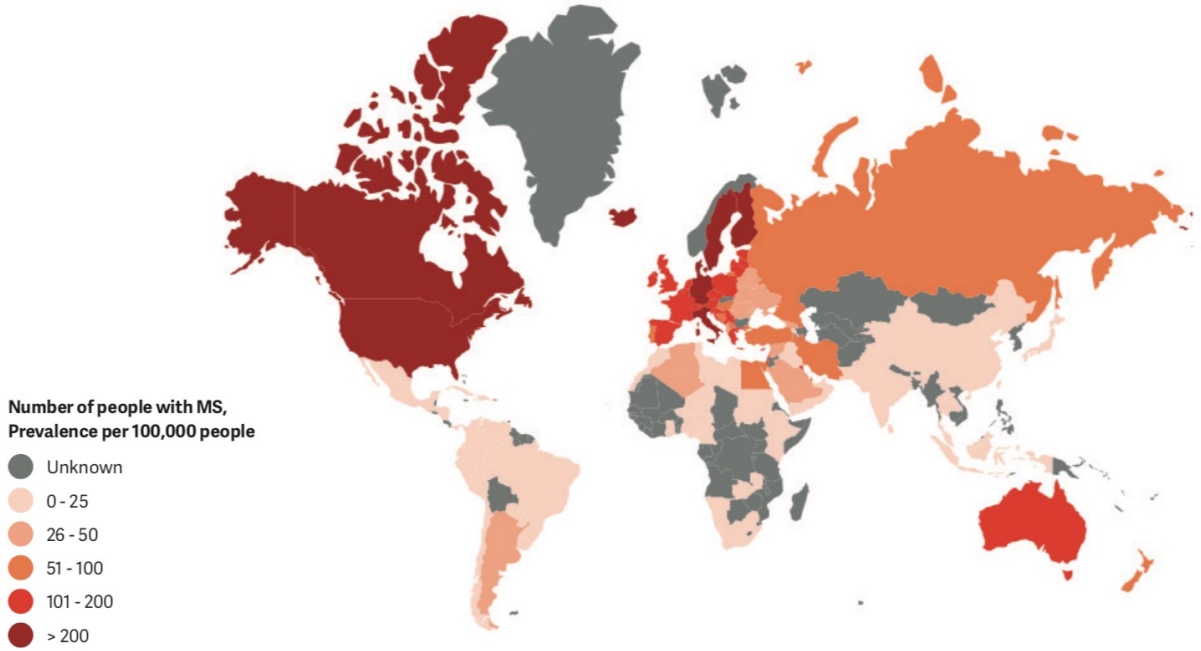
MRI

Pregnancy information



Why focus on pregnancy and women's health?

- ~2.8 million people globally (MSIF 2020)
- ~132/100,000 in Australia (~1/700)
- All ethnicities affected, although prevalence varies by ethnicity/race
- Young people – typically diagnosed between 20-40 years of age



Expert Consensus on Pregnancy and Breastfeeding*

PRE-PREGNANCY COUNSELLING

Things you should know about fertility and pregnancy at diagnosis

PRENATAL ADVICE

Things to consider when pregnancy plans advance

PREGNANCY

Things to be aware of during pregnancy

POSTPARTUM

What should you know once a pregnancy has ended

Expert Consensus on Pregnancy and Breastfeeding*

PRE-PREGNANCY COUNSELLING

- All women with MS of child-bearing age should have pre-pregnancy counselling, ideally early on following MS diagnosis
- Women should be advised if considering pregnancy to discuss this with their MS team before trying to conceive

Expert Consensus on Pregnancy and Breastfeeding*

- Women with MS should be aware that MS does not affect fertility and contraception should be used if pregnancy undesirable

PRE-PREGNANCY COUNSELLING

- A few studies have looked at a hormone called Anti-Müllerian Hormone (AMH) that is associated with ovarian reserve i.e. the number of eggs that a woman has left
- The largest of these studies concluded that women with MS have equivalent levels of AMH to age-matched women without MS

But, women with MS still tend to have fewer children

Danish study comparing more than 9,000 women with MS to more than 37,000 women without MS

Cohort	Adjusted IRR	95% CI	p value
Live births before diagnosis			
Reference women	1.00		
Women with MS	0.91	0.89 – 0.94	<0.0001
Reference men	1.00		
Men with MS	0.98	0.94 – 1.01	0.20
Live births after diagnosis			
Reference women	1.00		
Women with MS	0.63	0.60 – 0.66	<0.0001
Reference Men	1.00		
Men with MS	0.69	0.65 – 0.74	<0.0001

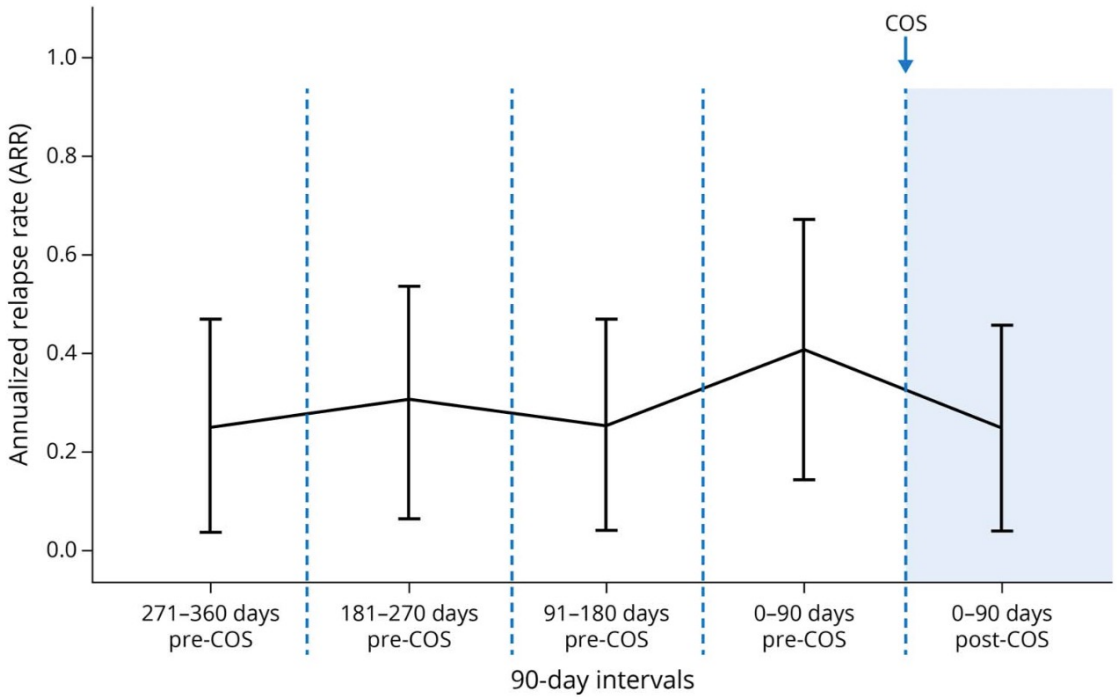
Moberg et al MSJ 2020; 26(8):902-911

Infertility is common in Australia

- Infertility affects about 1 in 6 Australian Couples
- In 2019 88,929 IVF cycles were started across Australia and NZ
- Resulted in 16,310 babies born (~18% success rate)

Assisted reproductive technology

Figure 2 Annualized Relapse Rate 3 Months Post-COS vs 12 Months Pre-COS for All Cycles (n = 80)



COS = controlled ovarian stimulation.

65 women included
37% of fertility treatment cycles resulted in a pregnancy with a live birth

Graham et al Neurology, Neuroimmunol Neuroinflamm 2023; 10(3):1-13

What is the risk that your child will develop MS?

- The risk of your child also developing MS is very low
  - 2-3.5% chance if one parent has MS
  - ~20% chance if both parents have MS
- Genetics play a role, but environment and lifestyle are important too

Expert Consensus on Pregnancy and Breastfeeding*

PRE-PREGNANCY COUNSELLING

- Women with MS should be re-assured that pregnancy does not increase the risk of worsening disability in MS

Pregnancy does not increase the risk of disability worsening

Short-term effects:

- 5.6% of women saw an increase in measurable neurological disability in the year after birth[1]
- Previous report 13% of women saw an increase in measurable neurological disability in the year after birth[2]

Long-term effects:

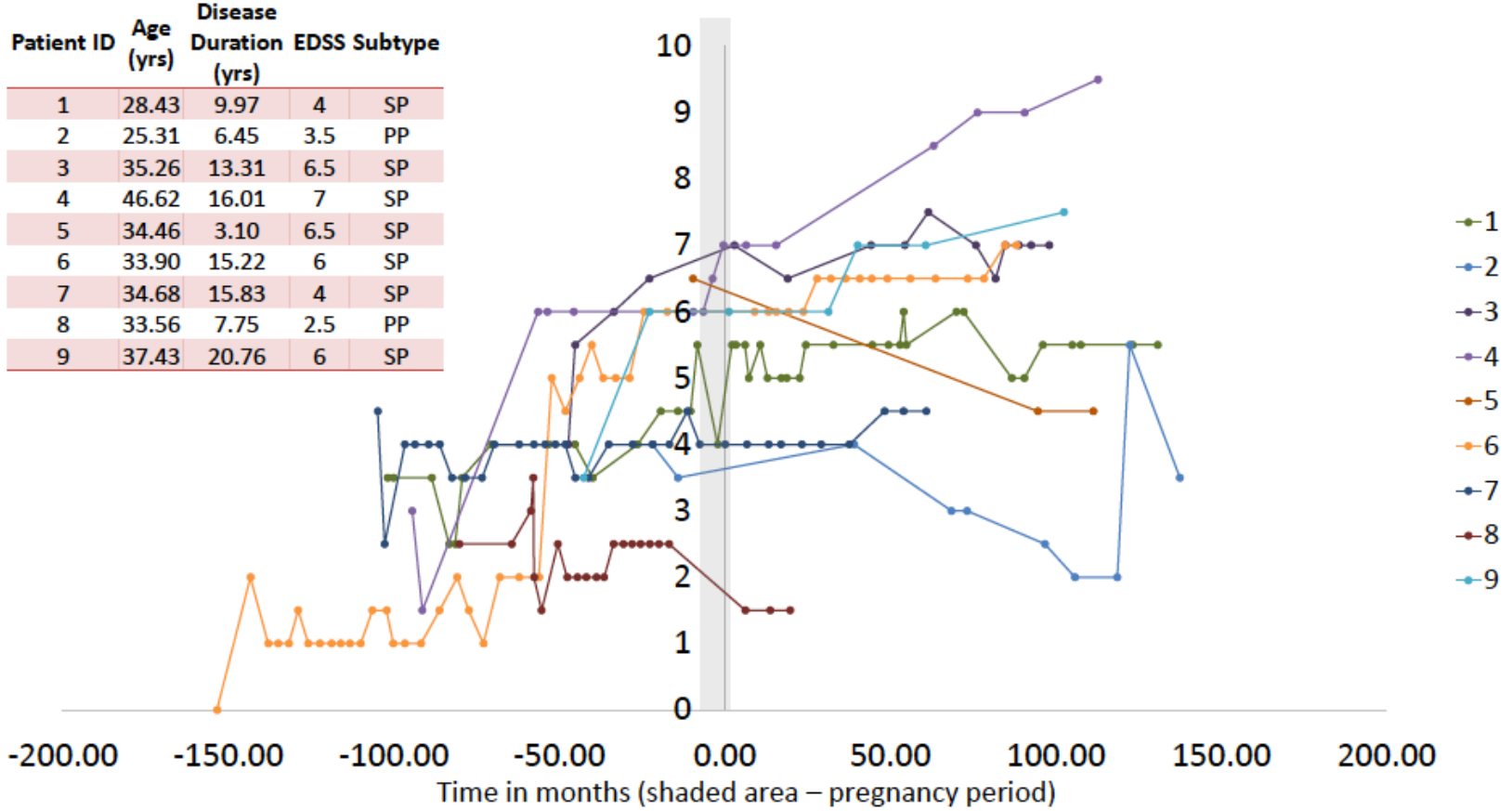
- Our work (1830 women) shows pregnancy after the onset of RRMS may be associated with less accumulation of disability[3]
- Spanish study found no impact of pregnancy and disability accumulation over the long-term[4]
- Window of opportunity for benefit <30 years, <5 years disease duration[5]

1. Yeh et al., Neurology, 2021; 96(24):e2989-3002. 2. Portaccio et al., JNNP 2014 85(8):845
3. Jokubaitis et al., Annals of Neurology 2016; 80(1): 89-100. 4. Zuluaga Neurology 2019; 92(13) e1507-1516 5. Zhu et al ECTRIMS 2023

What about pregnancy in progressive MS?

Long-term disability (EDSS) data was available for 9 MS patients with pregnancy during progressive phase

Patient ID	Age (yrs)	Disease Duration (yrs)	EDSS	Subtype
1	28.43	9.97	4	SP
2	25.31	6.45	3.5	PP
3	35.26	13.31	6.5	SP
4	46.62	16.01	7	SP
5	34.46	3.10	6.5	SP
6	33.90	15.22	6	SP
7	34.68	15.83	4	SP
8	33.56	7.75	2.5	PP
9	37.43	20.76	6	SP



Kister Mult Scler J 2016; 22(S3): 400-705

Expert Consensus on Pregnancy and Breastfeeding*

PRE-PREGNANCY COUNSELLING

- Women with MS should be aware that relapse rates may reduce during pregnancy, but increase in the three months postpartum and that the relapse rate during that year is the same as a woman with MS who is not pregnant

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 et al., NEJM 1998; 399(5):285-91

Expert Consensus on Pregnancy and Breastfeeding*

PRE-PREGNANCY COUNSELLING

- Women should not defer disease modifying treatment (DMT) if considering pregnancy in the future

- When prescribing or starting DMTs in women of childbearing age, MS teams should consider the likely timing of a planned pregnancy, the safety of all treatments during pregnancy as well as the risks associated with cessation of treatments, including rebound relapses and risk of postpartum relapse, to inform the choice of which DMT to commence

Expert Consensus on Pregnancy and Breastfeeding*

PRENATAL ADVICE

- Women with MS should be given the same prenatal advice as women without MS including advice to stop smoking and healthy living****
- Women should take prenatal supplements including Vitamin D and folic acid following normal obstetric advice

Expert Consensus on Pregnancy and Breastfeeding*

PRENATAL ADVICE

- ****New Study published 19 Nov 2023 A Danish nation-wide register-based cohort study
  - >789,000 women with >879,000 babies
  - Pregnancies between 1991 - 2018
  - Women who smoked during pregnancy had a 42% increased risk of developing MS (n=1,296)
  - Babies born to mothers who smoked during pregnancy had a 38% higher risk of developing MS later in life (n=110)

Nielsen et al, MSJ 19 Nov 2023 – epub ahead of print

Expert Consensus on Pregnancy and Breastfeeding*

PRENATAL ADVICE

- Women with MS currently on a DMT should have discussions with their neurologist and information on when to stop or whether to continue their DMT, depending on the individual safety profile of that DMT, combined with their disease activity and risk of relapse

- Women who plan to stop their DMT prior to conceiving should be aware of the average length of time from trying to conceive to conception in a woman of their age, and potential impacts on their MS of stopping their DMT

Expert Consensus on Pregnancy and Breastfeeding*

PREGNANCY

- Consider the whole person including mental health
- Many women find their MS symptoms improve during pregnancy; however, some symptoms may worsen, particularly in later pregnancy stages





Expert Consensus on Pregnancy and Breastfeeding*

PREGNANCY

- Pregnancy in women with MS should not automatically be considered a high-risk pregnancy
- Having MS should not influence obstetric management e.g. delivery method, however significant disability e.g. spasticity should be taken into account

Expert Consensus on Pregnancy and Breastfeeding*

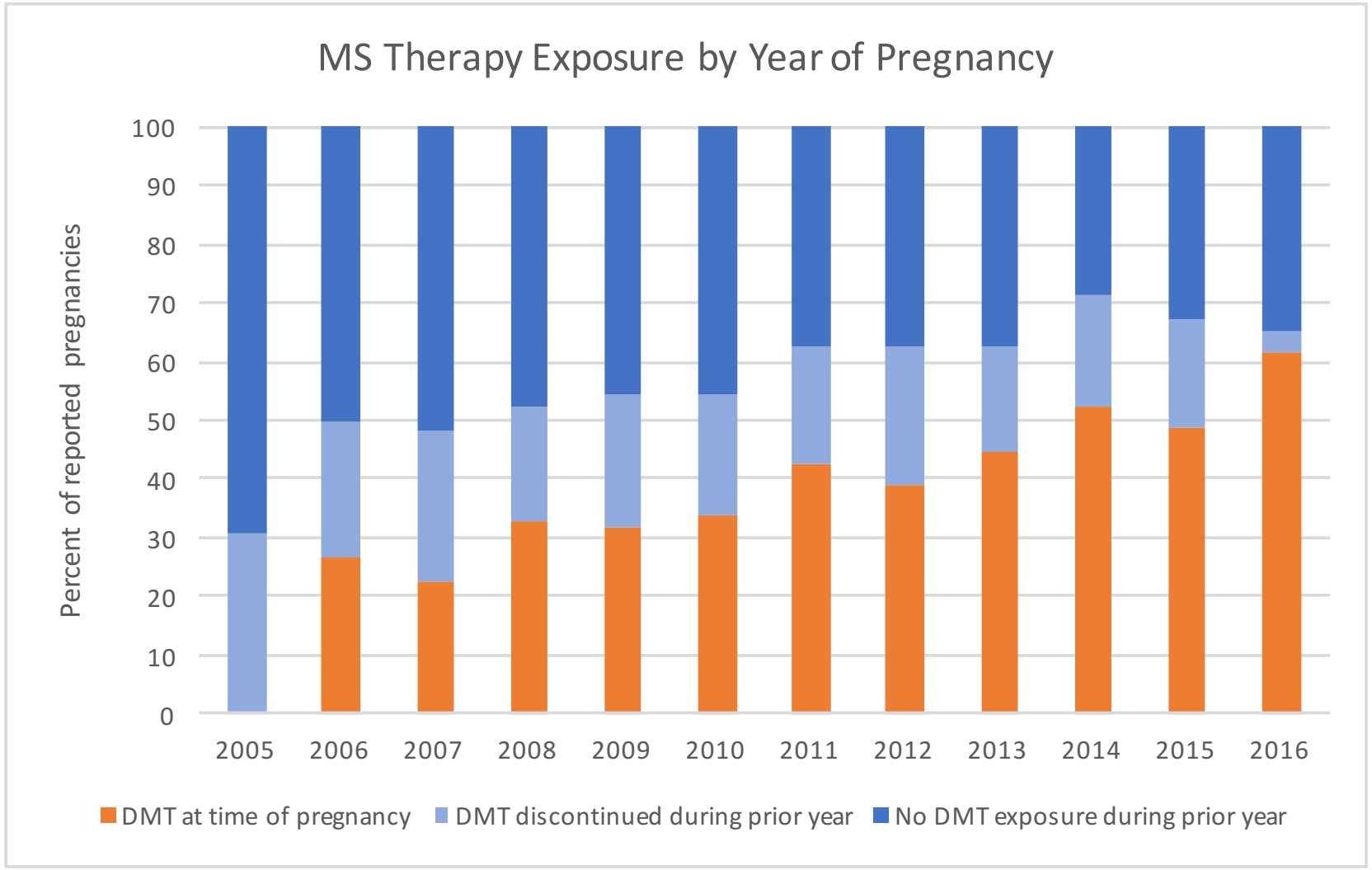
PREGNANCY

- Some DMT are safe to use in pregnancy, and should be considered in women with highly active MS. Alternatively, planned pre-pregnancy use of DMT with a long-lasting effect may provide effective disease control during pregnancy whilst minimising drug exposure during this period*

MS DMT and pregnancy exposure

- Exclusion of pregnant women from clinical trials
- Choice between “themselves” i.e. take DMT to control your MS OR “their child” i.e. stop taking DMT during pregnancy and breastfeeding
- Lack of data
- Information largely from clinical Registries

MS DMT exposure in pregnancy



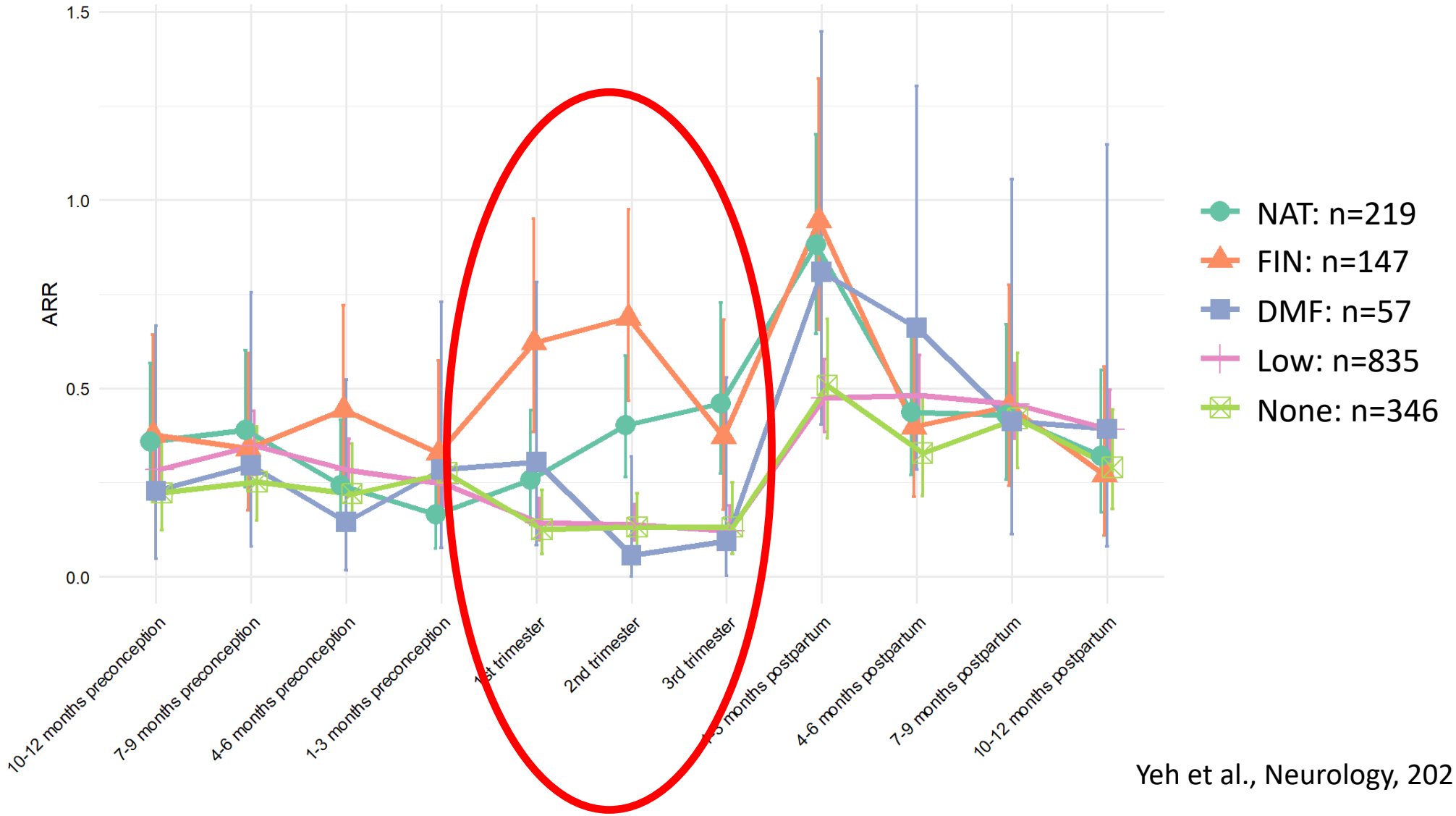
Nguyen et al, MSARD 2019; 28:235-243

DMT exposure and neonatal data

Krysko et al Lancet Neurology 2023; 22:350-366

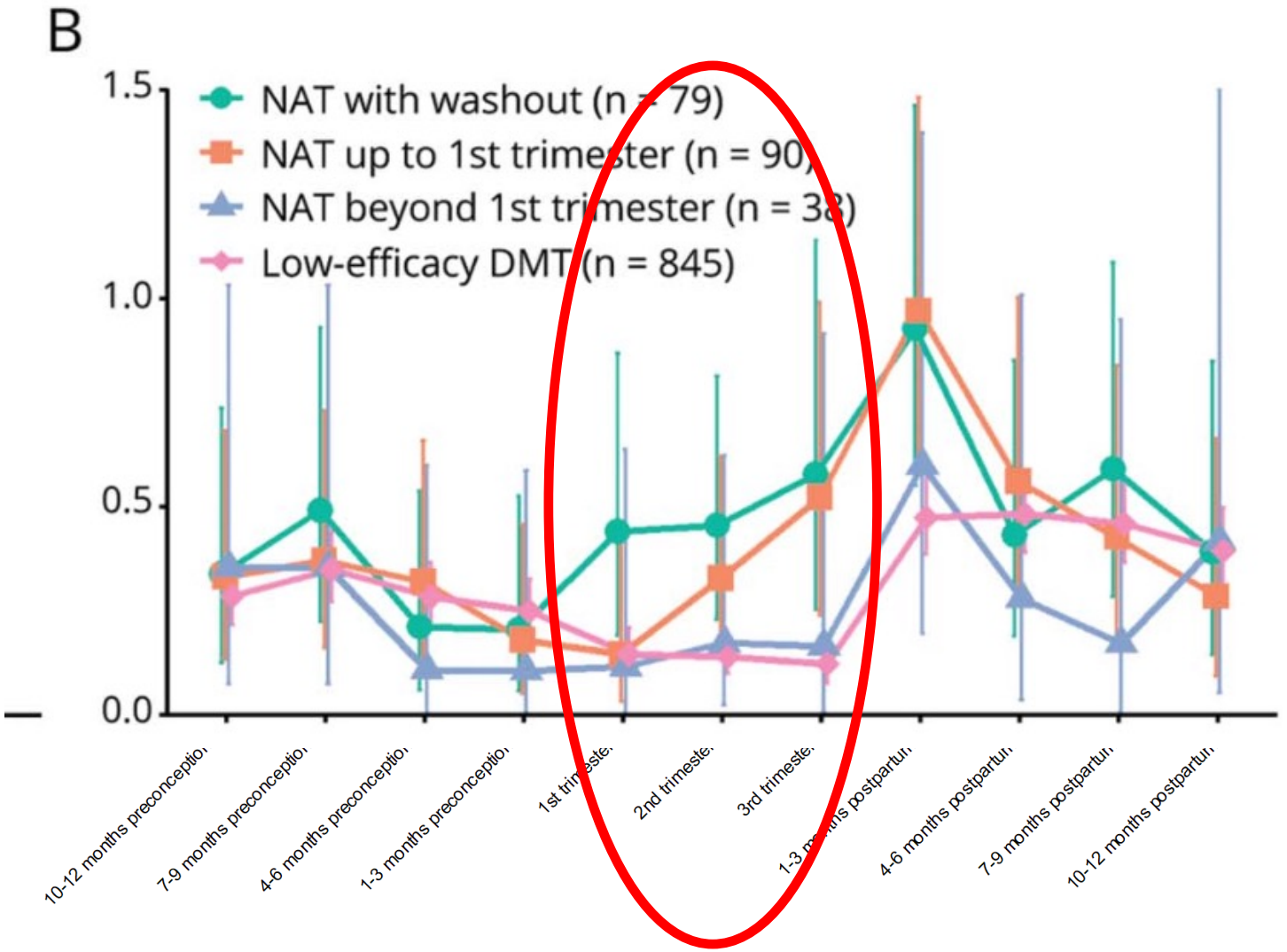
	Interferon-β or Copaxone	Tecfedera	Tysabri	Ocrevus	Kesimpta	Lemtrada	Gilenya, Mayzent, Zeposia, Ponvory	Mavenclad	Aubagio
Safe in pregnancy?	✓ No evidence of increased rate of malformations or abortions	✓ Stop with conception (EMA may continue in pregnancy if benefit outweighs risk)	✓ BUT must stop in 3rd trimester, last dose ~week 32-34 (extended dosing)	✓/✗ FDA 6 month washout** **attempt conception ~1 months after last dose (after next menstrual period)	✓/✗ FDA 6 month washout** **time monthly injection with period. Stop when pregnancy confirmed	✗ Minimum 4 month washout after last dose, and check thyroid function first. Elevated risk of miscarriage	✗ Minimum 2 month washout. Increased risk of malformations. Stop upon accidental exposure	✗ Men and women avoid conception for at least 6 months after last dose	✗ Suggested 2 year washout. Accelerated elimination in case of accidental exposure
n	>2500 women ea	>450 women	>500 preg	>250 preg	30 preg	233 preg	>800 fingo preg	16 preg w/in 6m	222 preg

Relapse in pregnancy



Yeh et al., Neurology, 2021; 96(24):e2989-3002

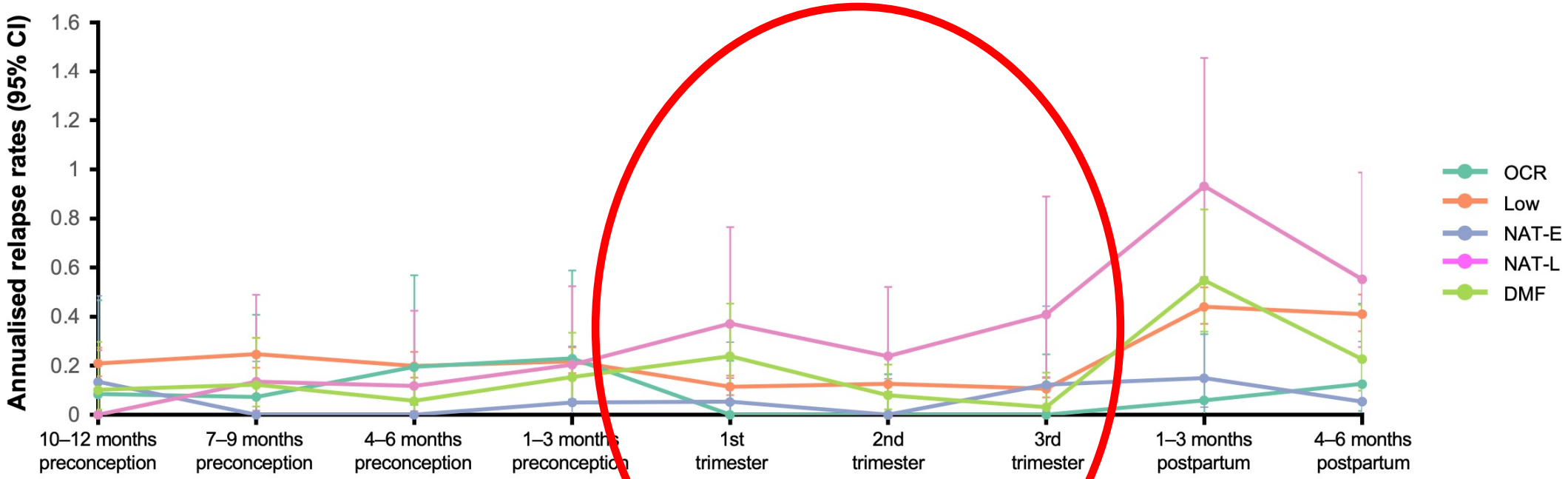
Relapse in pregnancy



Yeh et al., Neurology, 2021; 96(24):e2989-3002

Relapse in pregnancy

Minimal MS disease activity was observed in the first trimester postpartum among women treated with OCR



	10–12 months preconception	7–9 months preconception	4–6 months preconception	1–3 months preconception	1st trimester	2nd trimester	3rd trimester	1–3 months postpartum	4–6 months postpartum
OCR (N=73)	53	58	66	73	73	73	73	73	65
Low (N=1329)	1053	1145	1235	1329	1329	1329	1329	1322	1236
NAT-E (N=82)	66	71	78	82	82	82	82	82	78
NAT-L (N=82)	57	63	74	82	82	82	82	82	80
DMF (N=164)	123	137	149	164	164	164	164	164	144

Yeh et al., ECTRIMS 2023

Expert Consensus on Pregnancy and Breastfeeding*

PREGNANCY

- Corticosteroids can be used for treatment of relapse in pregnancy, methylprednisolone either orally or intravenously is the treatment of choice

- MRI is not contraindicated in pregnancy, but contrast should be avoided if possible. Routine scans can be deferred until after pregnancy.

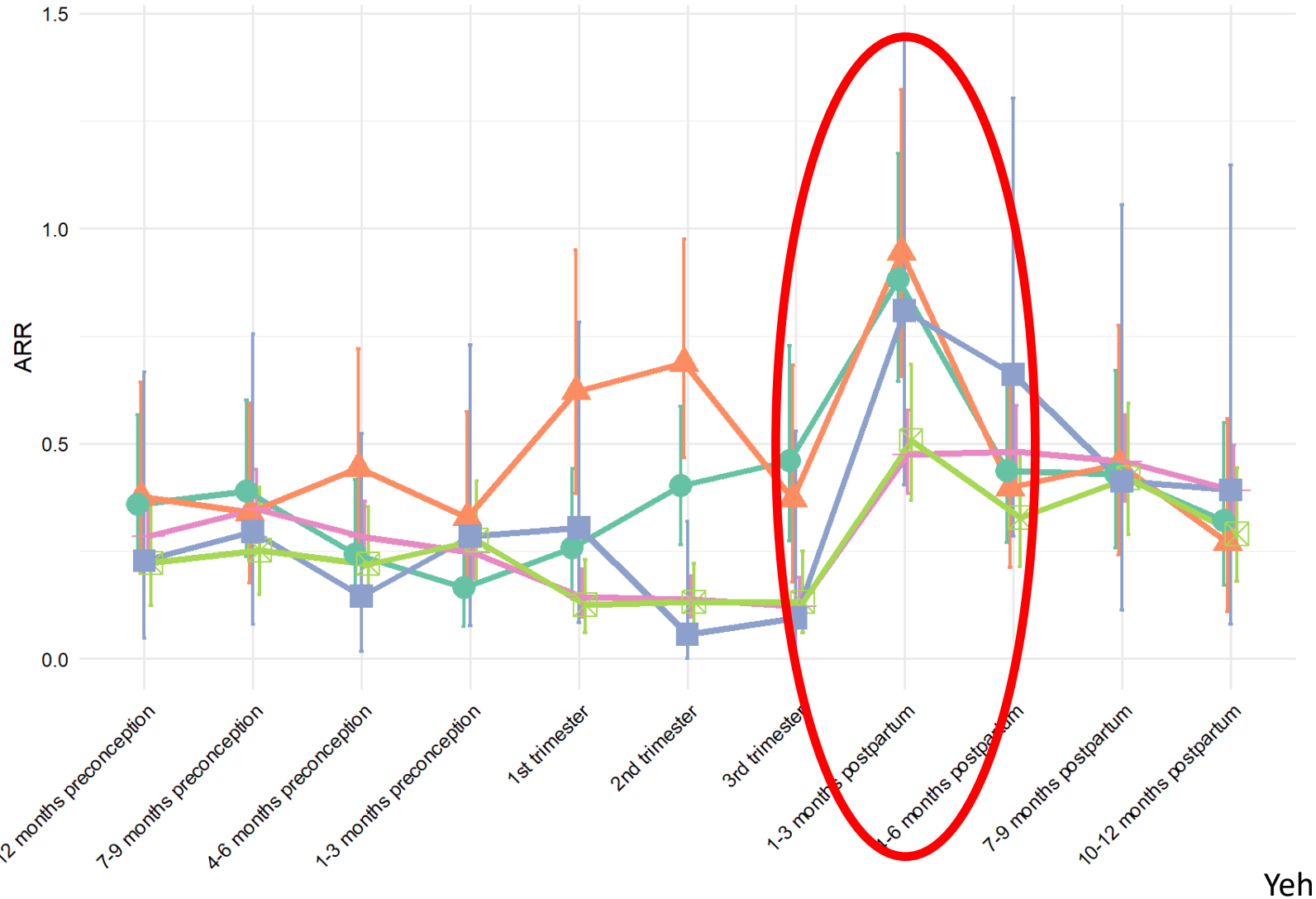
Expert Consensus on Pregnancy and Breastfeeding*

POSTPARTUM

- Physiotherapy may help with pelvic floor rehabilitation after delivery.

- Women should be aware of a higher risk of relapse in the postpartum period; those women who are untreated during their pregnancies are equally at risk, as are women on higher efficacy DMT as compared to those on low efficacy therapies.

Postpartum relapse risk

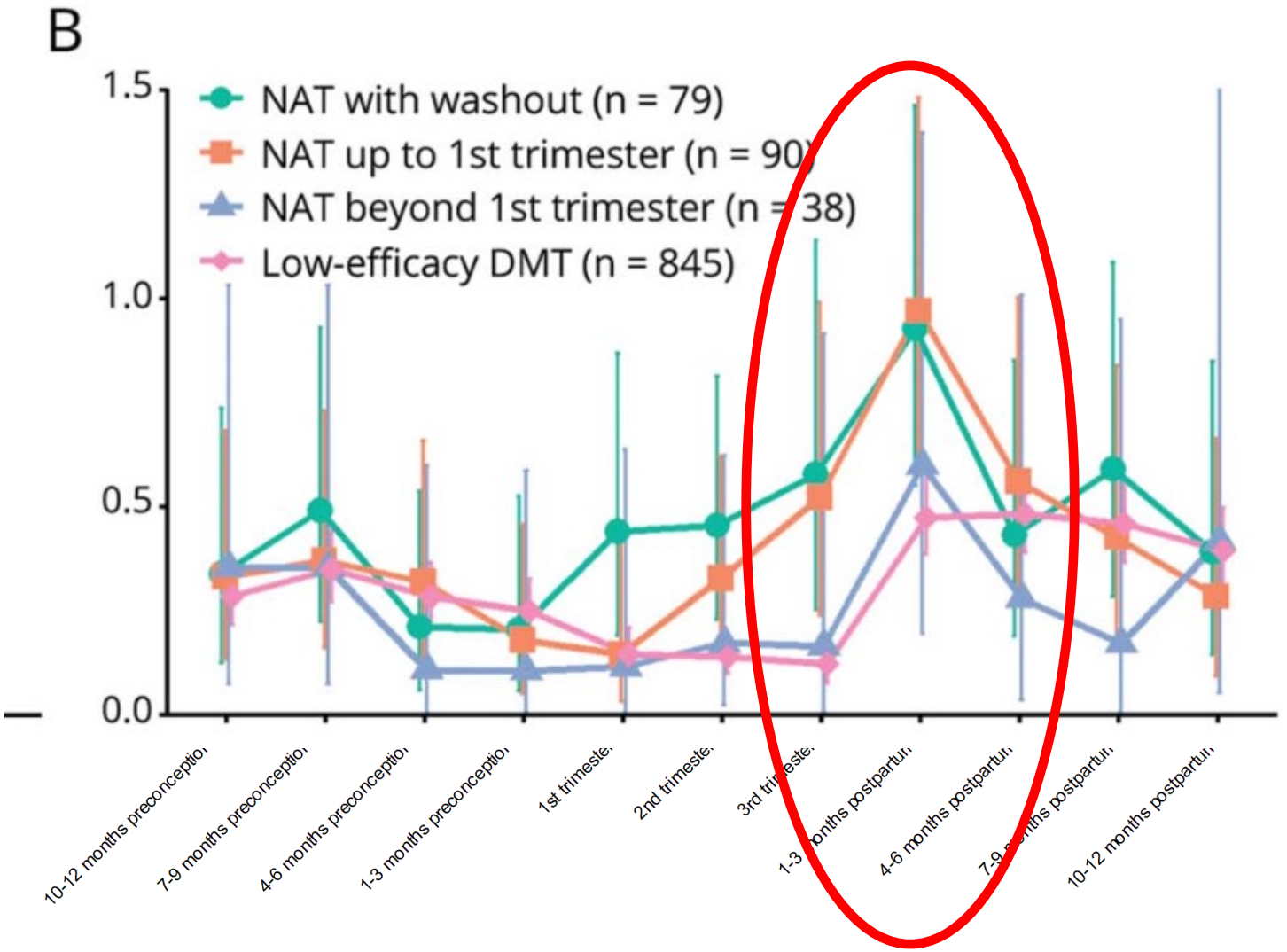


NAT: n=219
FIN: n=147
DMF: n=57
Low: n=835
None: n=346

13.6% of women had a postpartum relapse

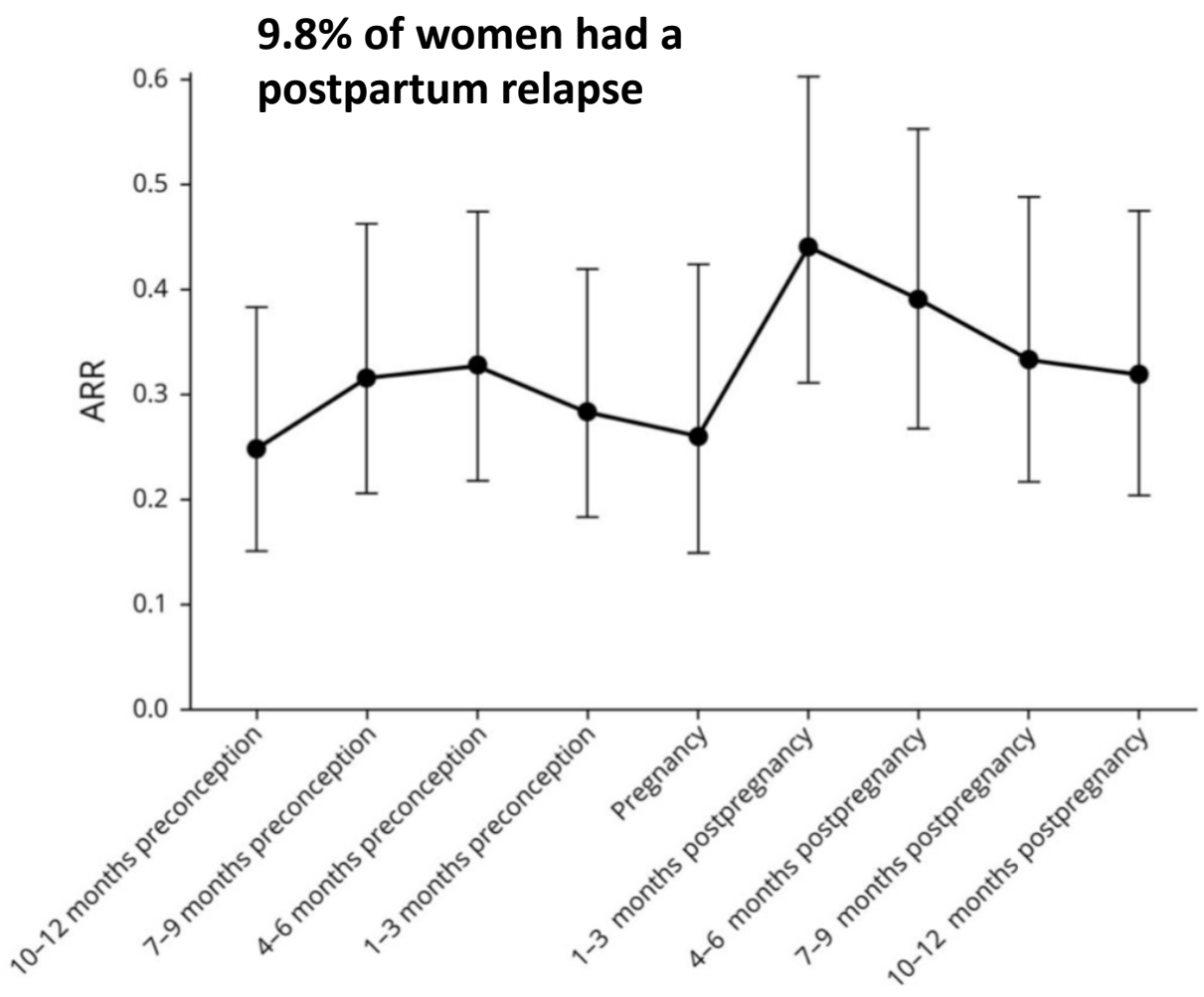
Yeh et al., Neurology, 2021; 96(24):e2989-3002

Postpartum relapse risk



Yeh et al., Neurology, 2021; 96(24):e2989-3002

Postpartum relapse risk – Abortions/Miscarriages/Stillbirths



Yeh et al., Neurology, 2021; 96(24):e2989-3002

Table 3 Poisson regression analysis: risk of postabortion relapses (n=188 events)

	OR	95% CI	P values
Age (each year)	1.02	0.98 to 1.06	0.41
Disease duration (each year)	0.98	0.95 to 1.01	0.23
EDSS score (each unit)	1.13	0.98 to 1.29	0.10
Preconception relapse rate (each unit)	1.32	1.03 to 1.68	0.026
Pregnancy duration (each week)	1.02	0.97 to 1.07	0.41
Comorbidities			
No (n=138)	1.00	0.56 to 1.14	0.21
Yes (n=50)	0.80		
No. of abortion			
First (n=153)	1.00	0.96 to 1.92	0.09
Second/third (n=35)	1.36		
Type of abortion			
Spontaneous (n=171)	1.00	1.20 to 2.64	0.004
Elective (n=17)	1.77		
Assisted reproductive techniques			
No (n=180)	1.00	0.25 to 2.28	0.62
Yes (n=8)	0.76		
Ongoing disease-modifying treatment			
No (n=102)	1.00	0.51 to 0.98	0.038
Yes (n=86)	0.71		

EDSS, Expanded Disability Status Scale.

Landi JNNP 2018; 89(12): 1272-1278

Expert Consensus on Pregnancy and Breastfeeding*

POSTPARTUM

- Rapid DMT re-initiation should be encouraged in women with active disease to reduce postpartum relapse risk
- Choice of DMT should be discussed with the clinical care team to weigh health and safety concerns.

Expert Consensus on Pregnancy and Breastfeeding*

POSTPARTUM

- Women with MS should be encouraged to breastfeed due to the known benefits to mother and baby
- Women should be aware there is some evidence that breastfeeding may be beneficial in terms of preventing postpartum relapse in women with less active MS

Expert Consensus on Pregnancy and Breastfeeding*

POSTPARTUM

- Women should be aware that some DMTs would be considered safe to use whilst breastfeeding, whereas others are not safe, and for some there is currently insufficient evidence for their safety.

DMT and Breastfeeding

Krysko et al Lancet Neurology 2023; 22:350-366

	Interferon-β	Copaxone	Tysabri	Ocrevus Rituximab	Kesimpta	Aubagio	Tecfidera	Gilenya	Mavenclad	Lemtrada
Transfer to breast milk	✓	?	✓	✓	?	?	?	?	✓	?
Safe to use	✓	✓	✓	✓ Wait 4 hours after infusion	✓	✗	✗	✗	✗ Wait 10 days after last dose	?
n	<100	<100	20	Ocre 23 women Ritux 17	0	0	2	0	1	0

Expert Consensus on Pregnancy and Breastfeeding*

POSTPARTUM

- MS teams should give advice about storing breast milk in freezer in case of fatigue or relapse

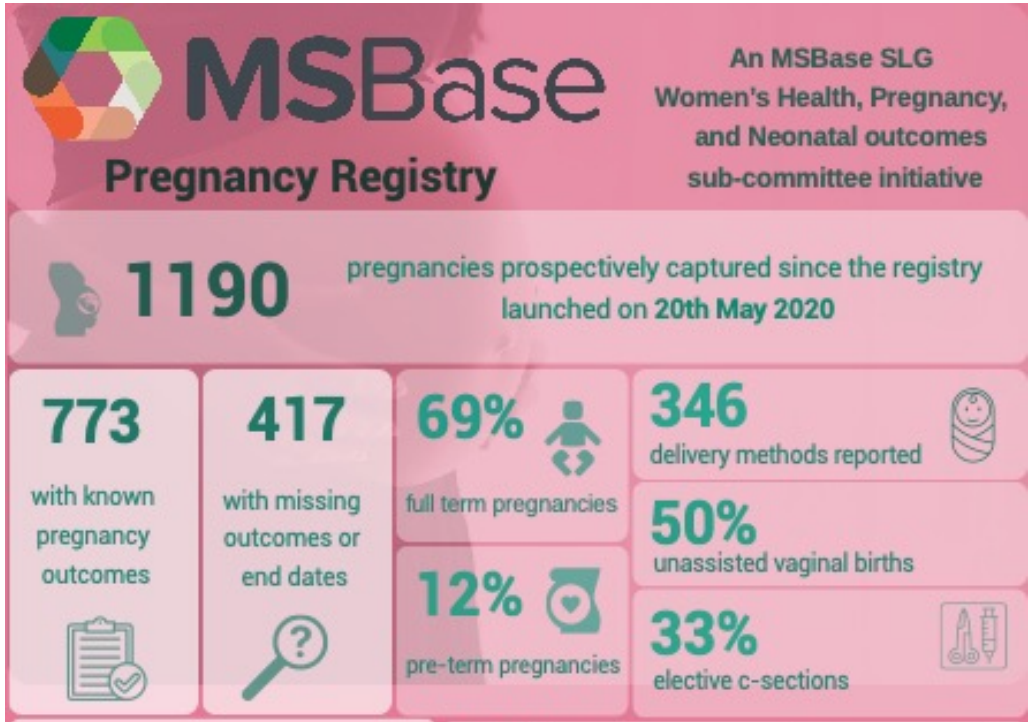
- Women should be aware that there is no indication to stop breastfeeding if methylprednisolone is required to treat a postpartum relapse, however, they should wait for 4-8 hours after steroids are given before they breastfeed.

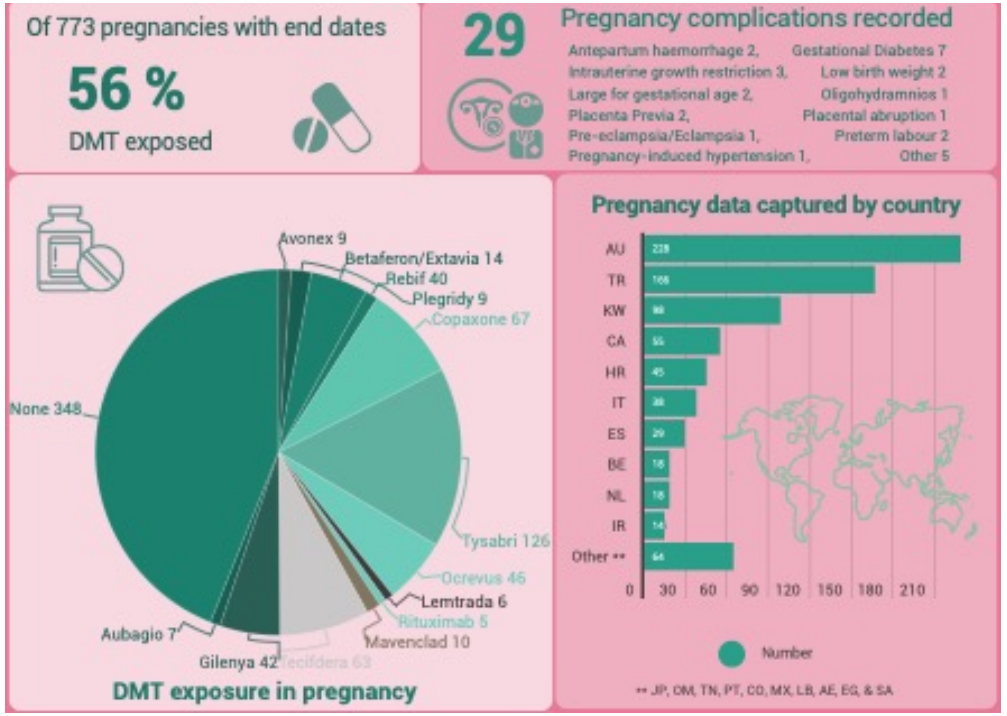
How can you contribute to knowledge?

Therapeutic Advances in Neurological Disorders

The MSBase pregnancy, neonatal outcomes, and women's health registry

Vilija G. Jokubaitis, Olga Skibina, Raed Alroughani, Ayse Altintas, Helmut Butzkueven, Sara Eichau, Yara Fragoso, Kerstin Hellwig, Stella E. Hughes, Louise Rath, Anneke van der Walt and Orla Gray, on behalf of the MSBase Scientific Leadership Group*



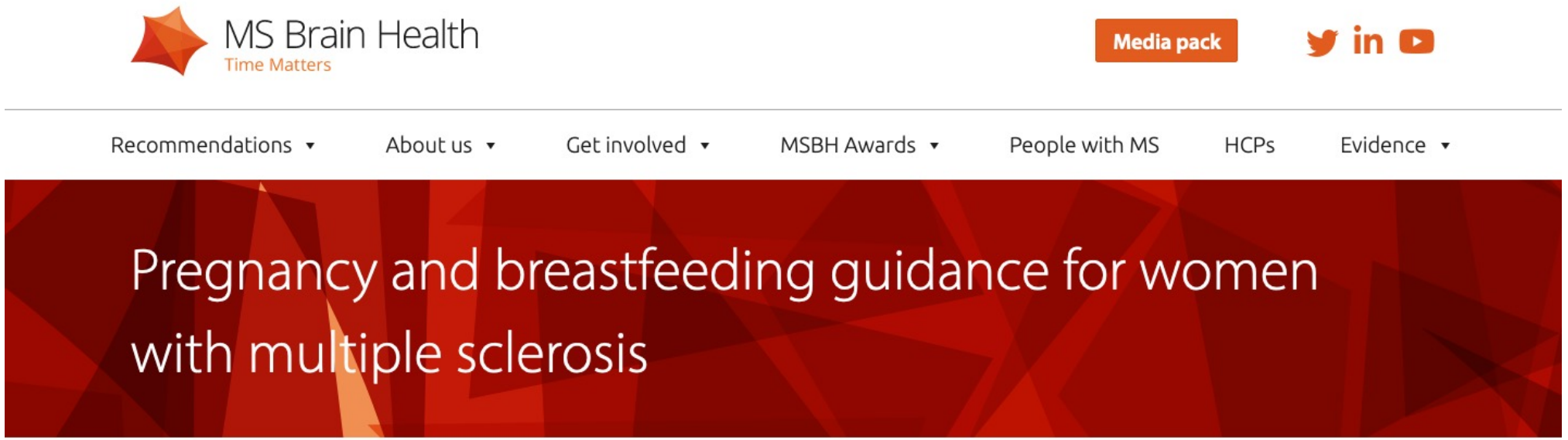


Take home messages

1. MS does not affect fertility
2. Your child has a very low risk of developing MS
3. Pregnancy planning should start early for women and men with consideration of which therapies are appropriate to use before, during and after pregnancy
4. Follow standard obstetric advice
5. Pregnancy is NOT harmful to the MS course
6. Relapse rates reduce for many women with MS during pregnancy
7. Pregnancy is still a time of disease activity risk for some women
8. Exclusive breastfeeding may reduce the risk of postpartum relapse in some women
9. Lots that we don’t know about the effect of DMT on neonatal outcomes

Online Guidelines

https://www.msbrainhealth.org/evidence/pregnancy-and-breastfeeding-guidance-for-women-with-multiple-sclerosis/



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Royal Brisbane and Women's Hospital
Flinders Medical Centre (Adelaide)
Royal Hobart Hospital

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