Pregnancy and a rare neuroimmune diagnosis

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QUESTIONS:

I. Pregnancy effects on neuroimmune disease?

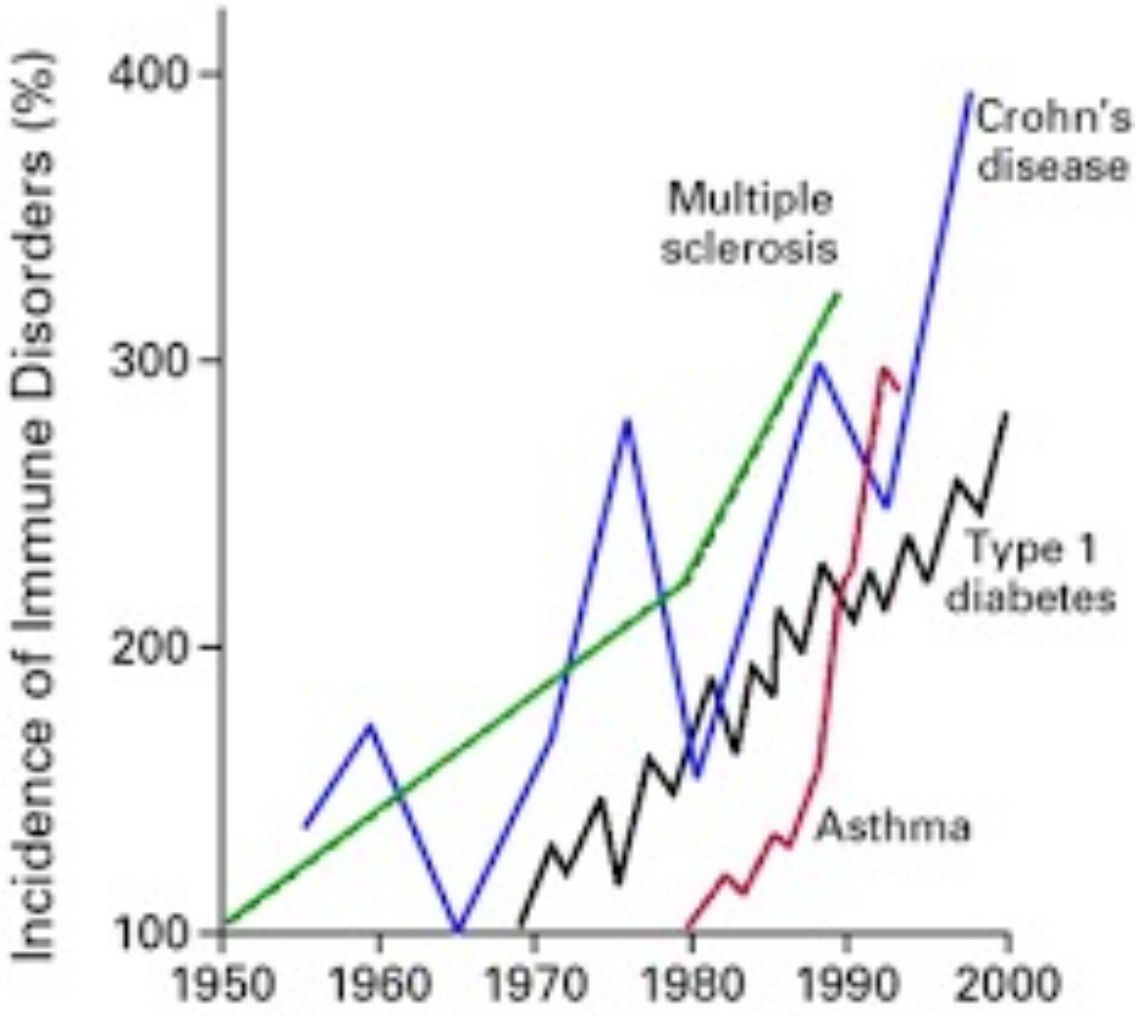
II. Neuroimmune disease effects on pregnancy?

III. Questions about delivery and breastfeeding?

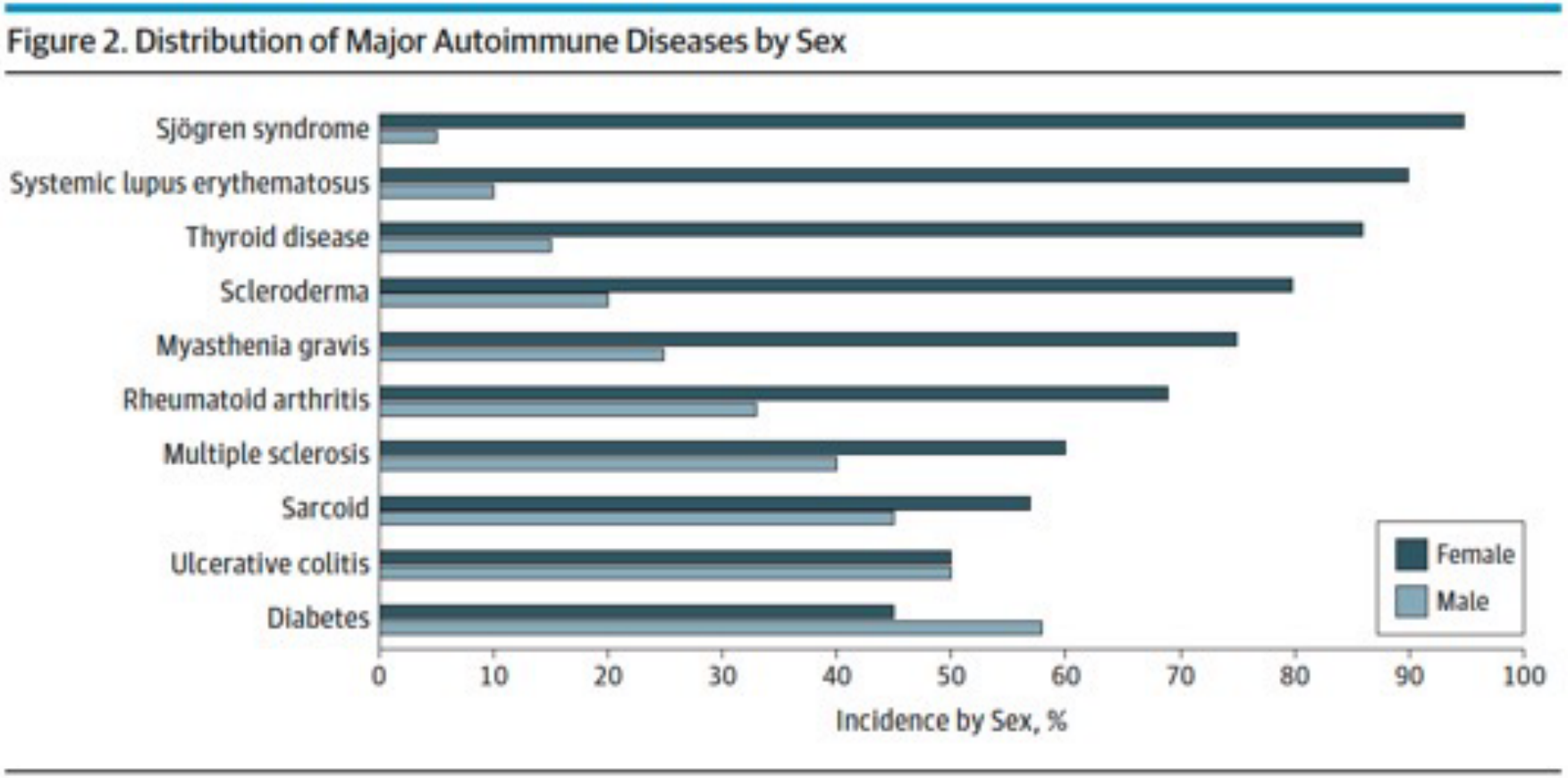
IV. Treatment considerations for pregnancy and baby?

Increase in autoimmune diseases over the past 5 decades

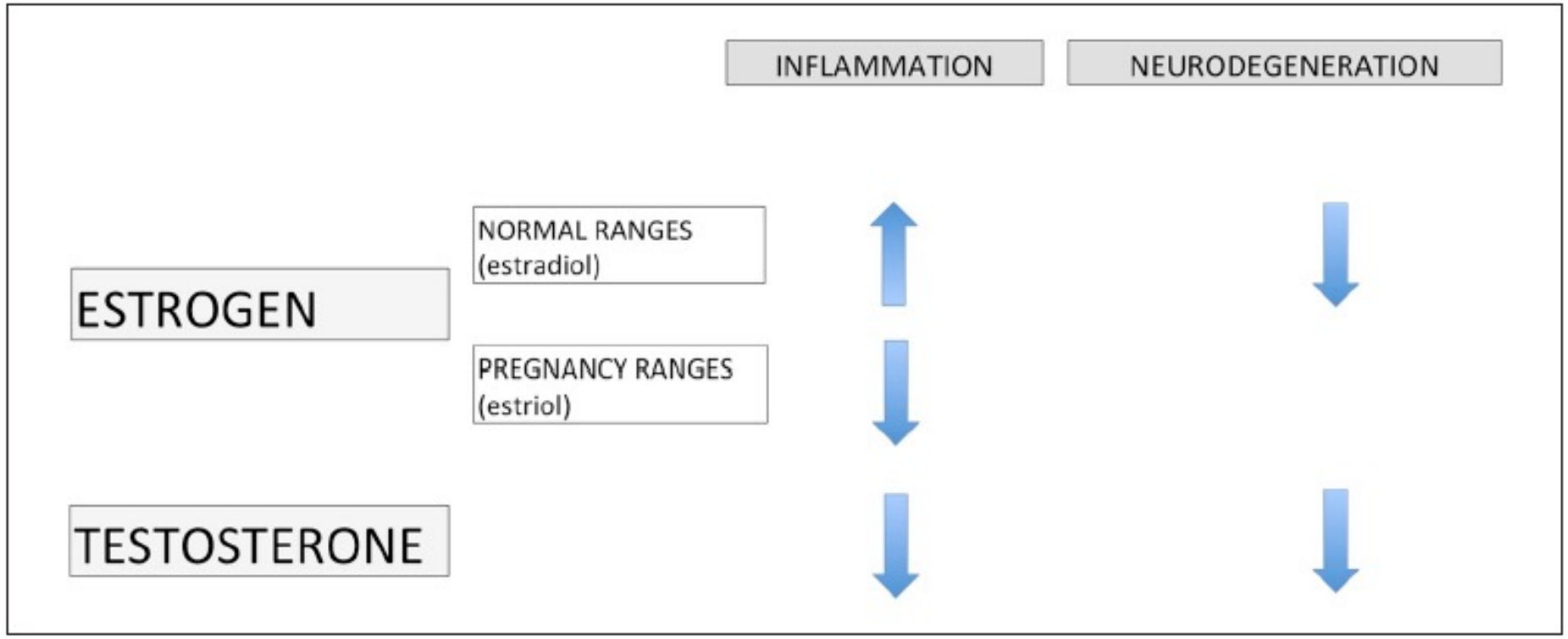
NIH: 24 million affected by autoimmune diseases



Increase in female:male ratios in autoimmune diseases

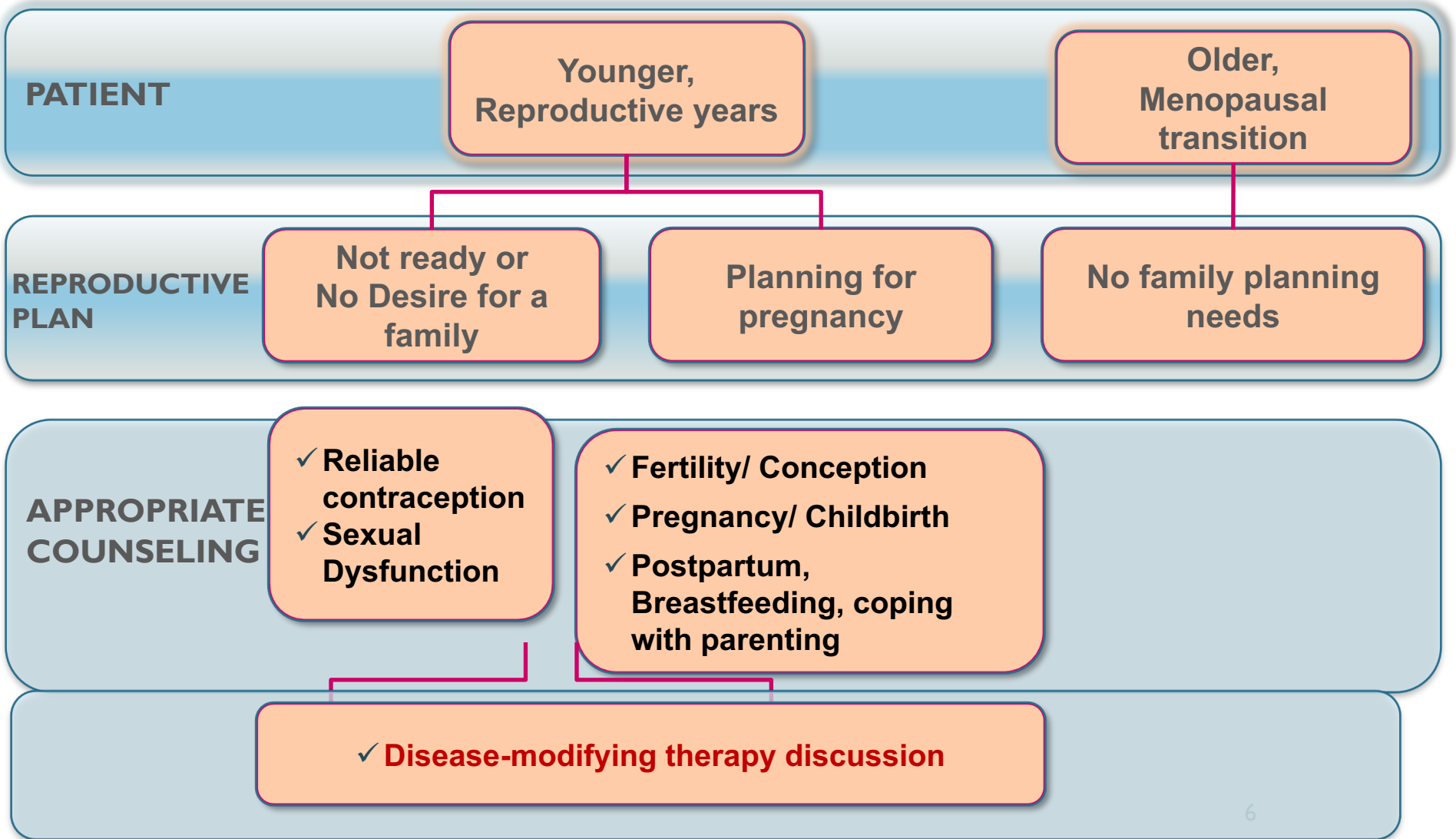


Sex hormone paradigm in autoimmune diseases



Bove and Chitnis, MSJ 2014

Individualized Reproductive Counseling



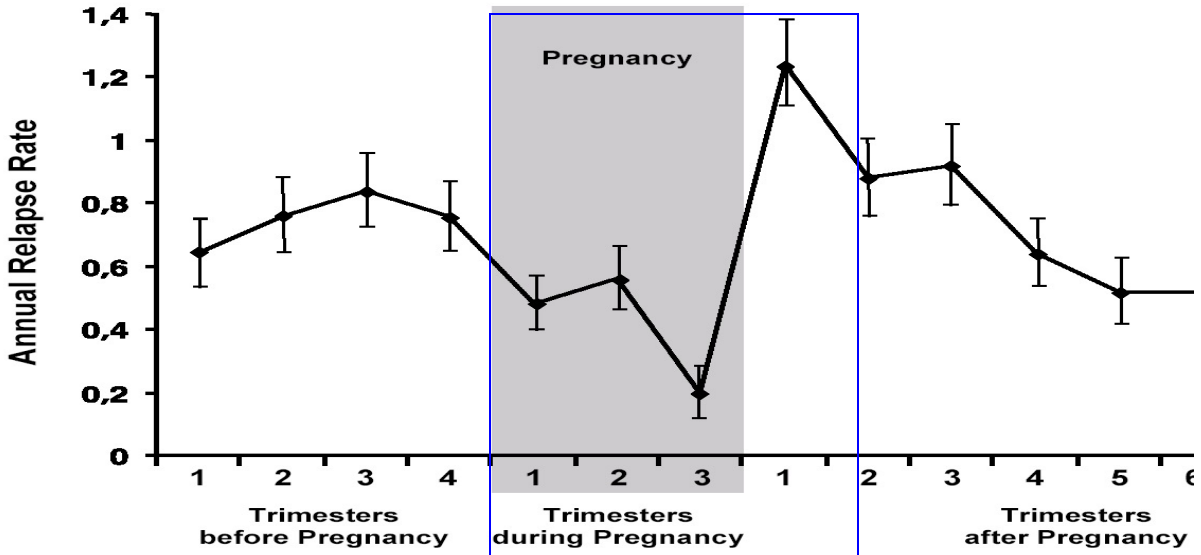
Considering pregnancy?

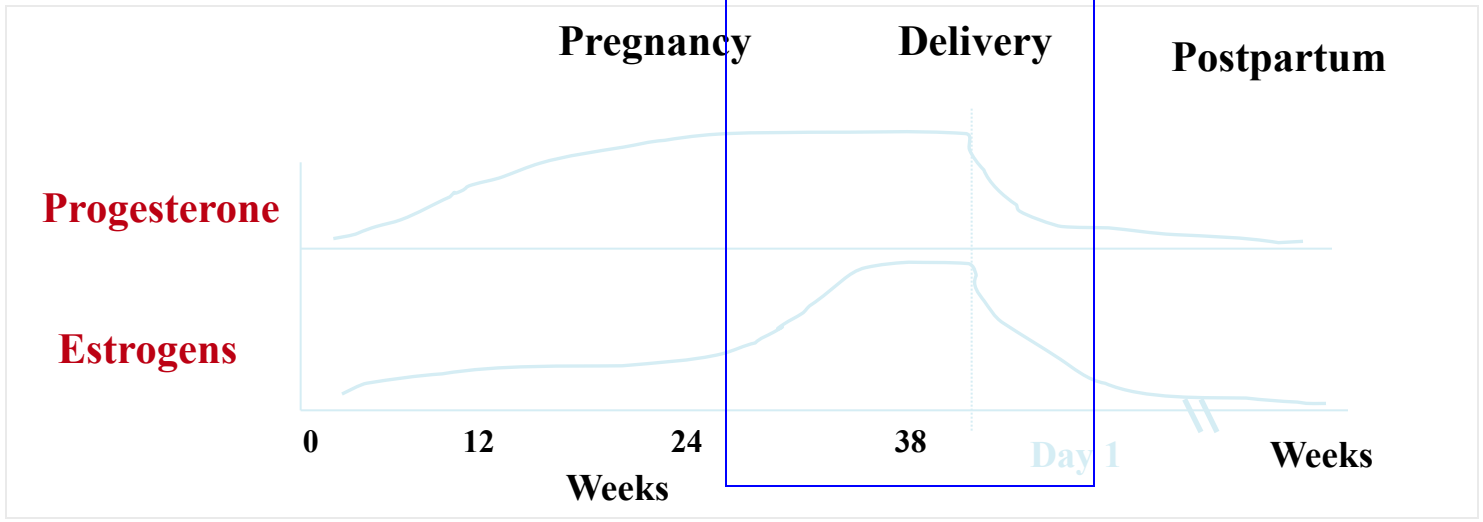
- Referral to high risk Obstetrician
- OB should be in communication with treating neurologist
- Medication timing/stopping should be planned ahead of trying to conceive
- Consider artificial reproductive treatment (ART) if no conception > 6 months

1. Effect of pregnancy on the course of neuroimmune diseases

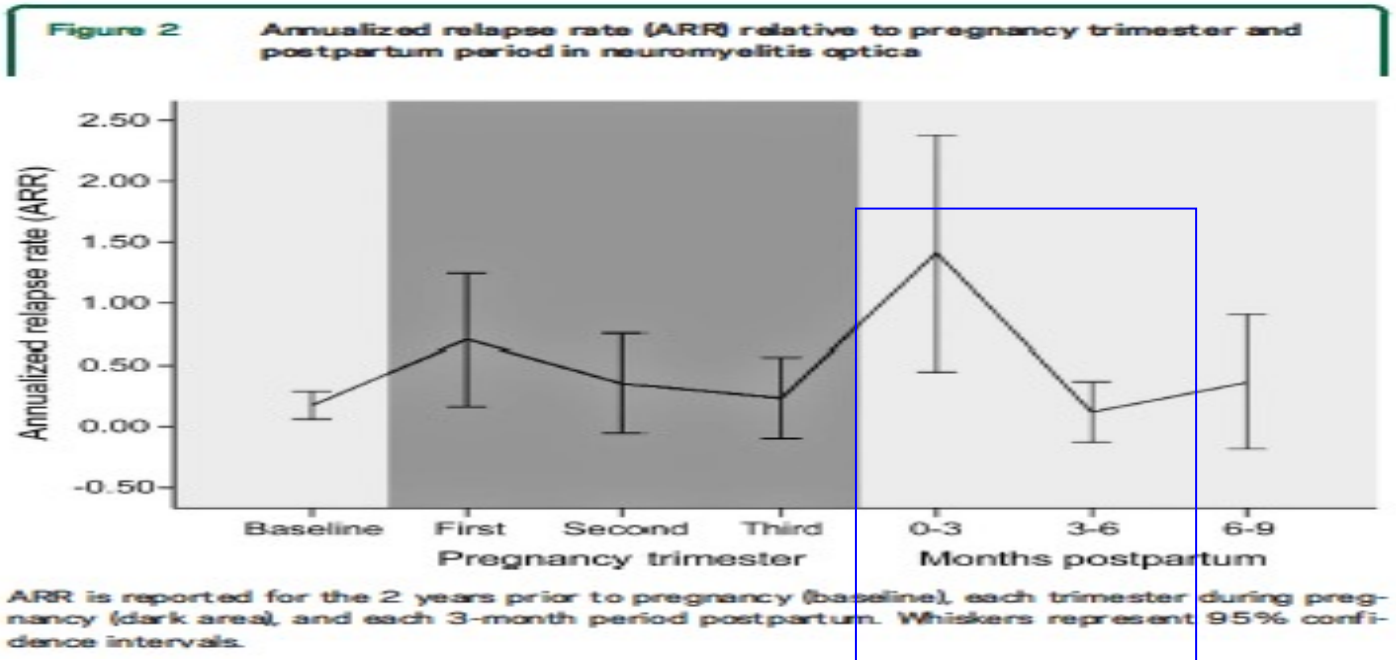
Multiple Sclerosis (MS): Decreased relapses in the third trimester; Increased relapses in the 3 months postpartum

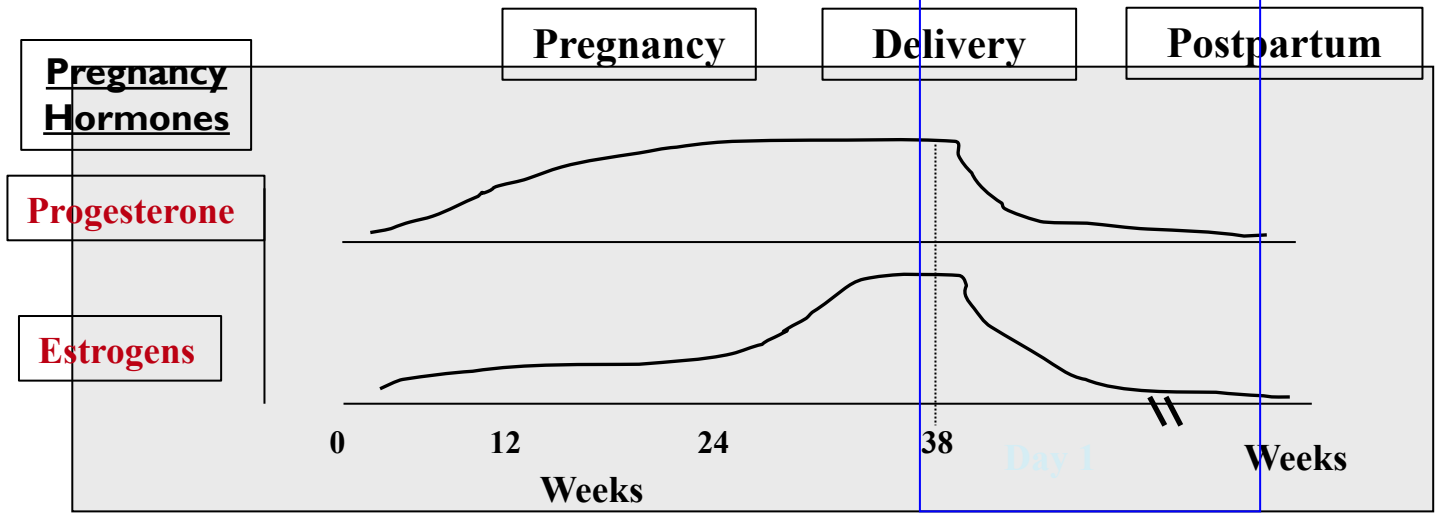
MS Relapse Rates





NMOSD Relapse Rates increase postpartum – correlates with change in sex hormones





Klawiter, Neurology 2017

Relapse Rates increase postpartum in NMO-SD

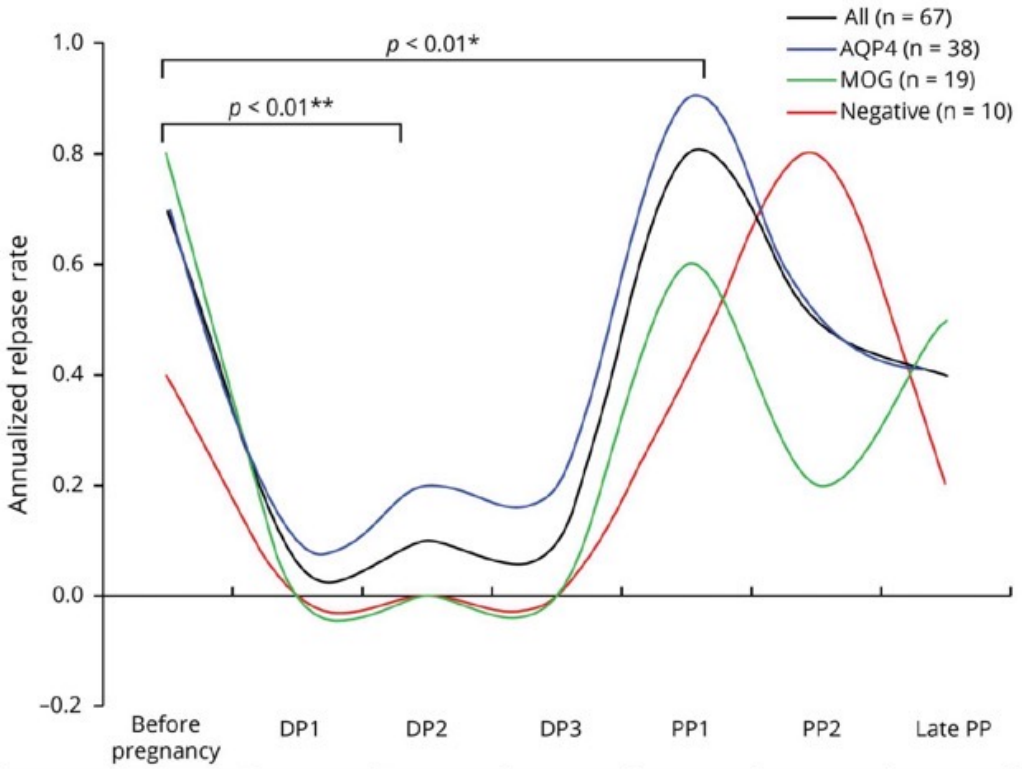
Table 1 Relapse rates in different phases of pregnancy among patients with neuromyelitis optica (NMO)

Study	Country	Patient diagnosis	Patients (pregnancies), n	AQP4-IgG+	Relapse rates, mean ± SD								
					Before pregnancy	First trimester	Second trimester	Third trimester	0-3 Months postpartum	3-6 Months postpartum	6-9 Months postpartum	9-12 Months postpartum	12-24 Months postpartum
Bourre et al, *Neurology*, 2012[14]	France	NMO	20 (25)	Not reported	1.0 ± 0.09	0.5 ± 0.06	0.5 ± 0.06	1.2 ± 0.1	2.2 ± 0.09	0.8 ± 0.06	1.1 ± 0.09		1.2 ± 0.03
Kim et al, *Neurology*, 2012[10]	Korea	NMOSD	40 (54)	All	0.38	0.15	0.31	0.46	2.0	1.38	0.62		Not reported
Shimizu et al, *Mult Scler*, 2015[11]	Japan	NMOSD	22 (22)	All	0.57 ± 1.16	0.66 ± 1.35	0.49 ± 1.21	0.17 ± 0.74	1.80 ± 2.04	0.80 ± 1.64	0.63 ± 1.47	Not reported	Not reported
Nour et al, *Neurology*, 2016[13]	United Kingdom, Portugal, Japan	NMOSD	20	All	0.133	Not reported	Not reported	Not reported	1.60	Not reported	Not reported	Not reported	Not reported

Abbreviations: AQP4 = aquaporin-4; IgG = immunoglobulin G; NMOSD = neuromyelitis optica spectrum disease.

V. Davoudi, MD, et al. Neurol Neuroimmunol Neuroinflamm 2016 (Review)

Relapse Rates in MOGAD and double-seronegative NMOSD



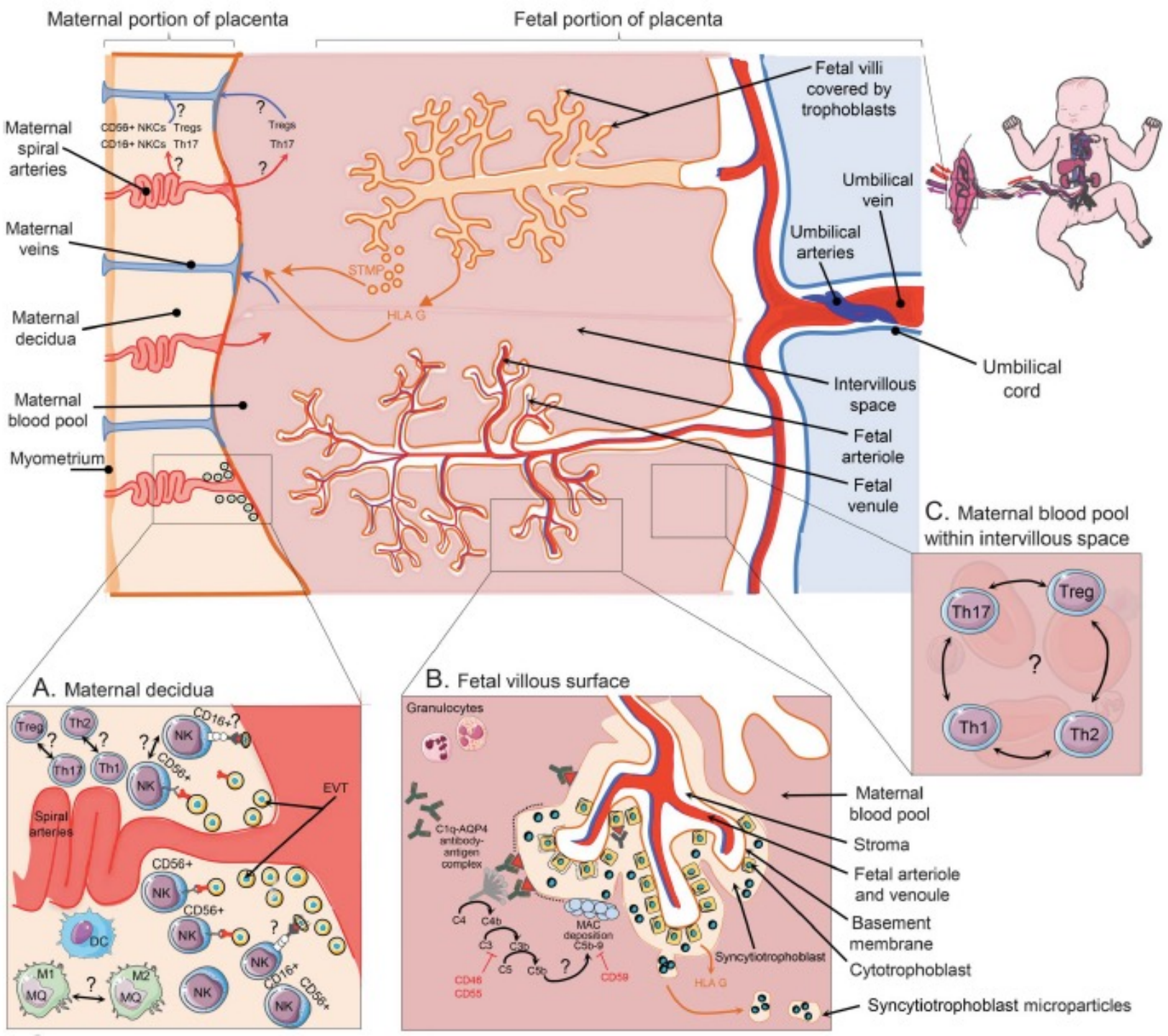
	Before pregnancy	DP1	DP2	DP3	PP1	PP2	Late PP
All (mean ± SD)	0.7 ±0.9	0.05 ± 0.49	0.1 ± 0.7	0.1 ± 0.7	0.8 ± 1.7	0.5 ± 1.3	0.4 ± 0.9
AQP4 (mean ± SD)	0.7 ± 0.9	0.1 ± 0.6	0.2 ± 0.9	0.2 ± 0.9	0.9 ± 1.9	0.5 ± 1.35	0.4 ± 0.9
MOG (mean ± SD)	0.8 ± 1.2	0	0	0	0.6 ± 1.5	0.2 ± 0.9	0.5 ± 1.1
Negative (mean ± SD)	0.4 ± 0.5	0	0	0	0.4 ± 1.2	0.8 ± 1.6	0.2 ± 0.6

*ARR of PP1 compared to ARR of the 12 months before pregnancy. **ARR of pregnancy (DP1, DP2, and DP3) compared to ARR of the 12 months before pregnancy. DP = during pregnancy, corresponding to first (DP1), second (DP2), or third trimester (DP3); PP = postpartum, corresponding to first trimester (PP1), second trimester (PP2), or between 6 and 12 months after delivery (late PP).

1. Summary: Effect of pregnancy on the course of neuroimmune diseases

- Most neuroimmune diseases are associated with an increased risk of relapse post-partum
- Consider restarting DMT post-partum or a course of steroids (may need to forgo breast-feeding)

II. Effect of neuroimmune disease on pregnancy



Davoudi, Bove, Chitnis; Neurol Neuroimmunol Neuroinflamm 2016

Does neuroimmune disease associated with pregnancy complications?

- MS – no complications
- NMOSD – higher rates of miscarriage and pre-eclampsia
- MOGAD – not enough data

Pregnancy outcomes in NMOSD patients

- Of 85 pregnancies reported in 40 patients with NMOSD 11 pregnancies **(12.9%)** in 6 participants were terminated by **miscarriage**.

- The rate of **preeclampsia** was significantly higher in NMO than the general population13 (**11.5%** vs 3.2% respectively).

Nour MM, et al. Neurology 2016

Rates of pregnancy-associated complications in NMOSD

Table 2 Rate of obstetric complications in pregnant patients with neuromyelitis optica (NMO)

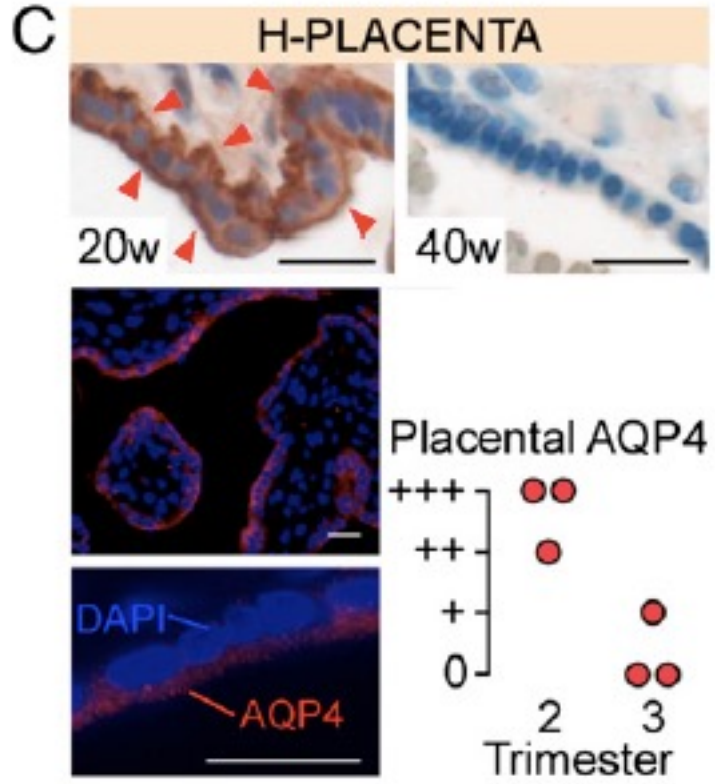
References	Country	Patient diagnosis	AQP4-IgG+	Total no. of pregnancies	Elective abortion	Spontaneous abortion	Stillbirth	Preterm delivery	Preeclampsia or pregnancy-induced hypertension	Low birthweight
Bourre et al, *Neurology*, 2012[14]	France	NMO	Not reported	38	5 (13.1)	8 (21)	Not reported	Not reported	Not reported	Not reported
Kim et al, *Neurology*, 2012[10]	Korea	NMOSD	All	54	13 (24)	1 (1.8)	0	1 (1.8)	Not reported	Not reported
Shimizu et al, *Mult Scler*, 2015[11]	Japan	NMOSD	All	22	1 (4.5)	1 (4.5)	1 (4.5)	1 (4.5)	1 (4.5)	1 (4.5)
Fragoso et al, *J Neurol*, 2013[12]	Brazil	NMO	Not reported	17	0	1 (5.8)	0	1 (5.8)	1 (5.8)	Not reported
Nour et al, *Neurology*, 2016[13]	United Kingdom, Portugal	NMOSD	All	85	Not reported	11 (12.9)	0	Not reported	Not reported	Not reported
	United Kingdom, Portugal, Japan	NMOSD	All	113	Not reported	Not reported	Not reported	Not reported	13 (11.5)	Not reported

Abbreviations: AQP4 = aquaporin-4; IgG = immunoglobulin G; NMOSD = neuromyelitis optica spectrum disease.
Values are n (%).

V. Davoudi, MD, et al. Neurol Neuroimmunol Neuroinflamm 2016 (Review)

AQP4 expression in the placenta

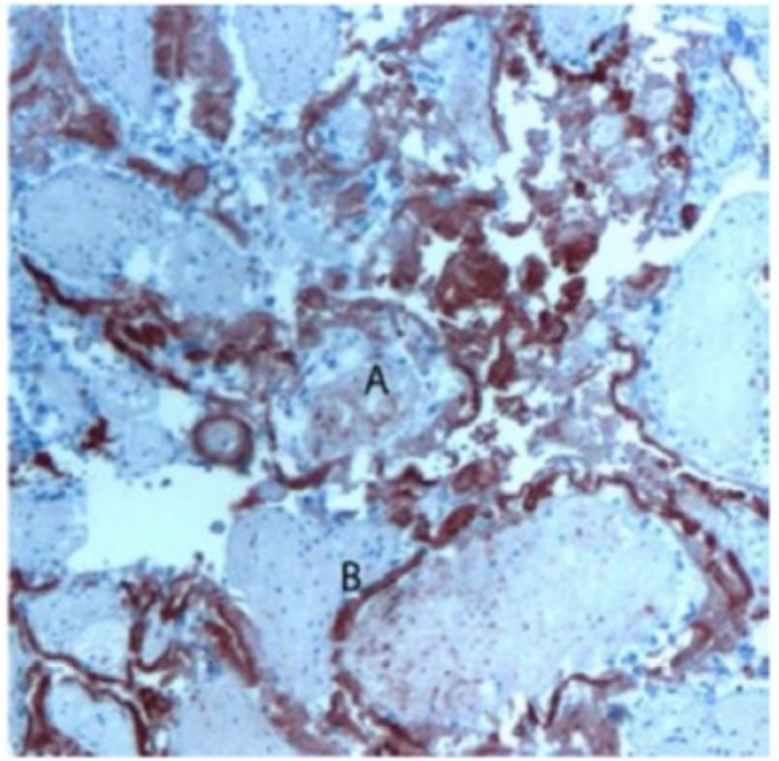
- Expression of AQP4 in placenta of a normal pregnancy:
  - High during the **second** trimester
  - Declines markedly in the **third** trimester



Samira Saadoun, et al. J Immunol 2013 De Falco M , et al. In Vivo 2007

Histopathology of placenta a pregnant patient with NMO

- A case report described:
  - A miscarriage in the second trimester of a patient with NMO
  - Placenta contained several regions of necrosis
  - Diffuse deposits of membrane attack complexes
    - mostly in perivascular areas of syncytiotrophoblasts.



Diffuse, mainly perivascular deposits (red staining) of the membrane attack complex of the complement system detected with an antibody to the C9neo epitope. Fetal vessels show moderate markings (A) and the phagocytic syncytiotrophoblast (a crucial interface for maternal-fetal placental transfer processes) is clearly marked (B)

Tara Lamont, et al. BMJ 2009

II. Summary: Effect of neuroimmune diseases on pregnancy outcomes

- AQP4 antibody positive NMOSD is associated with an increased risk of miscarriage and pre-eclampsia
  - Requires close monitoring and OB who is familiar with these complications
  - Unclear if medication changes these risks

III. Effect of Treatment on pregnancy and baby

DMT Management prior to conception

- Discuss cessation of treatment prior to attempting conception (0 days, 2 months, many months, depending on half-life ($T_{1/2}$) of the medication)
- Discuss optimization of conception chances: charting, basal body temperature measurement, use of ovulation kits, with goal to decrease time off therapy while trying to achieve pregnancy
  - Referral to infertility clinic if no pregnancy achieved after 3-6 months of optimal conception attempts, as opposed to 12 months' recommendation in a non-disease patient
- Consider stabilizing active patient with alternative therapy before initiating conception attempts
- Consider monthly IV steroids timed to menses in an active patient off therapy, while attempting conception

Decision point – should I stop DMT prior to/at pregnancy?

- Consider age– younger age more likely to relapse at discontinuation
- Consider prior disease activity, relapse rate
- Timing

- Current DMT half-life, MOA, PK and PD effects, risk of rebound disease activity

Decision point – should I stop DMT prior to/at pregnancy?

- Available data is observational
- Pregnancy registries for most disease modifying therapies
- Recommend to join a pregnancy registry to increase our knowledge about treatment effects in pregnancy

Drugs and placental transport:

- Monoclonal antibodies - During the 2nd trimester, transplacental transport of antibodies observed

- Small molecules – variable transport

FORMER FDA PREGNANCY CATEGORIES

Pregnancy Category	Description
Category A	• Adequate and well-controlled human studies have failed to demonstrate a risk to the fetus during the first trimester • No evidence of risk in later trimesters
Category B	• No adequate and well-controlled studies in pregnant women • Animal studies have not demonstrated a risk
Category C	• No adequate and well-controlled studies in pregnant women • Animal studies have shown an adverse effect on the fetus • Potential benefits may warrant use of the drug in pregnant women despite potential risks
Category D	• Studies in humans have demonstrated adverse reactions leading to human fetal risks • Potential benefits may warrant use of the drug in pregnant women despite potential risks
Category X	• Studies in animals or humans have demonstrated adverse reactions leading to fetal abnormalities • Risks involved in the use of the drug in pregnant women clearly outweigh potential benefits

NEW FDA PREGNANCY DISCLOSURES

- Full discussion of risks and benefits of possible medication exposure in pregnancy, to mother and fetus
- Disclosure of known preclinical and clinical data related to pregnancy exposure of any new drug
  - disease-associated maternal and/or embryo/fetal risk
  - dose adjustments during pregnancy and the postpartum period
  - maternal adverse reactions, fetal/neonatal adverse reactions, and/or the effect of the drug on labor or delivery.

FDA goal: to support health care providers' understanding of drug product risks and benefits and to facilitate informed prescribing decisions and patient counseling.

Risk vs. benefit

General population risk of sponataneous abortions: 10-20%
General population risk of fetal malformations: 2-4%

Rituximab in pregnancy

- The terminal half-life of rituximab is on average 8-22 days, but it has been found at detectable levels in the blood of some patients for at least 24 weeks

- 102 pregnancies with rituximab use within 6 months of conception:
  - 78 resulted in live births and 12 in spontaneous abortions.
  - Of 54 live births with reported gestational age, 31 occurred at term (37 weeks+) and 2 before 32 weeks.
  - When checked, B-cell counts were low in 39% of newborns and normalized within 6 months.

Das et al, Rituximab before and during pregnancy: A systematic review, and a case series in MS and NMOSD. Neurol Neuroimmunol Neuroinflamm. 2018 Mar 19;5(3)

Ocrelizumab in pregnancy

- Recent ocrelizumab approval as therapy for RRMS and PPMS (2018)
- The half-life of Ocrelizumab is 26 days, therefore it is eliminated within 4 months.
- 81 pregnancies with maternal exposure to Ocrelizumab were reported from human studies in multiple sclerosis, rheumatoid arthritis and systemic lupus erythematosus patients,
  - 22 pregnancies with known outcome were exposed in utero within 3 months of conception.
  - Most of these pregnancies were terminated electively
  - 8 resulted in healthy babies
  - one infant with trisomy 21 was observed.

- Vukusic S, et al. An Update on Pregnancy Outcomes Following Ocrelizumab Treatment in Patients With Multiple Sclerosis and Other Autoimmune Diseases. 34th Congress of the European Commitee for Treatment and Research in Multiple Sclerosis (ECTRIMS); 10 - 12 October Berlin, Germany2018.

Tocilizumab in pregnancy

- Slightly increased risk of miscarriage, pre-term birth
- 12 month washout recommended

Newer medications:

- **Satralizumab** – may be similar to tocilizumab – more data needed.

- **Eculizumab** has been shown to be safe and effective for pregnant patients with paroxysmal nocturnal hemoglobinuria (PNH) (Kelly R, British journal of haematology 2010)

Mao-Draayer, Nature Reviews Neurology, 2019

Steroid use peripartum

- Trying to conceive: Prophylaxis - Consider: one dose iv steroids at menstrual period

- During pregnancy – steroid effects on fetus
  - 1st trimester – possible cleft lip
  - 2nd trimester – possible increased birthweight
  - 3rd trimester – possible increased birthweight

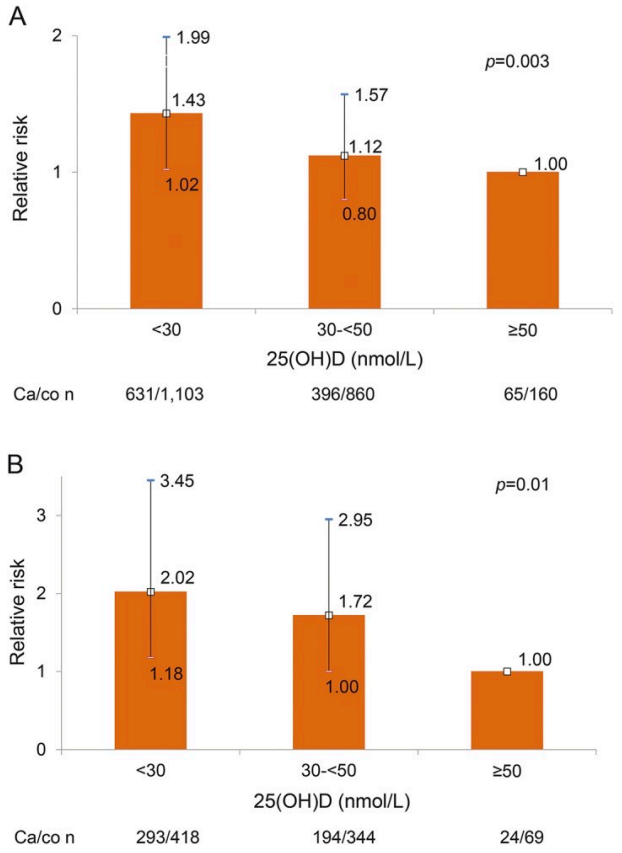
  Less than 10% of the maternal dose of prednisone, prednisolone, and methylprednisolone reaches the fetus as a result of metabolism to inactive forms by the placenta - the potential teratogenic effect of these inactive forms is uncertain.

  In contrast, betamethasone and dexamethasone do cross the placenta with minimal metabolism.

- IVIG is safe for use during pregnancy and may provide some benefit (Ferraro, 2004)

Vitamin D intrapartum

- Lowered Vitamin D levels during pregnancy has been associated with increased risk of MS in offspring
  - A 50 nmol/L increase in 25(OH)D was associated with a 39% reduced risk of MS (RR 0.61, 95% CI 0.44-0.85), p = 0.003.
  - Women with 25(OH)D levels <30 nmol/L had a 43% higher MS risk (RR 1.43, 95% CI 1.02-1.99, p = 0.04) as compared to women with levels ≥50 nmol/L. In women with ≥2 samples
  - MS risk was 2-fold higher in women with 25(OH)D <30 nmol/L as compared to women with 25(OH)D ≥50 nmol/L (RR 2.02, 95% CI 1.18-3.45, p = 0.01).



Munger, Neurology 2017
Munger, JAMA Neurology 2018

NMO Pregnancy management

- NMO pregnancies should be carefully monitored by OB and Neurology (high risk) for:
  - pre-eclampsia
  - miscarriage

- Consider immunosuppression through pregnancy if high pre-pregnancy relapse rate
- Strongly consider immunosuppression post-partum

- Pregnancy management review: Shosha, MSJ 2018

IV. Questions about delivery and breast feeding

Labor and Delivery

- Method of labor and delivery does not impact the post-partum course of MS
- Cesarean section to be considered in a woman with paraplegia, pelvic floor weakness, decreased/absent pelvic floor sensation
- Epidural anesthesia or general anesthesia, if required, has no effect on post-partum course of MS
- Consider stress-dose steroids for a woman with extended exposure to corticosteroids in pregnancy or pre-partum

Breast feeding

- Studies have shown some benefit in reduction of relapses if EXCLUSIVE BREAST-FEEDING (Langer-Gould, Arch Neurology 2009)
- Meta-analysis of studies of NON-EXCLUSIVE AND EXCLUSIVE breast-feeding found – reduction in relapses by 50% (Pakpoor, JN 2013)
- However studies are confounded by disease severity and choice to breast-feed!
- Take into consideration very active pre-partum disease course
- Post-partum depression management!!

Steroid use during breastfeeding

Drug	Excretion into breast milk	Considerations in Breastfeeding
Glucocorticoids	- Minimal (< accepted theoretical RID of 10%) - Peak levels 2 hours after dose	- Safe option - Wait 1 to max. 4 hours after dose before breastfeeding - Pump and dump on day of steroid infusion

Recommendations for DMT in women Breast-feeding with MS

	Recommendations for breastfeeding
Beta-interferon	EU/US: Limited data; consider the mother's clinical need and any potential adverse effects on the breastfed child
Glatiramer acetate	EU/US: Limited data; use caution when nursing
Natalizumab	EU: Do not use US: Use only if benefit outweighs potential risk to infant
Dimethyl fumarate	EU/US: Limited data; use caution when nursing
Ocrelizumab	EU: Do not use US: Use only if benefit outweighs potential risk to infant
Teriflunomide	EU: Do not use US: Use only if benefit outweighs potential risk to infant
Fingolimod	EU/US: Do not use
Alemtuzumab	EU: Discontinue during each course of treatment and 4 months after last infusion US: Limited data; discontinue either breastfeeding or therapy
Cladribine	Do not use

Coyle PK, Oh J, Magyari M, Orejia-Guevera, Houtchens, M. MSARD 2019

Postpartum management

- Postpartum – increased relapse risk – prophylaxis or relapse treatment
- Postpartum relapse risk related to pre-partum relapse rate – identify high risk patients!
- Postpartum iv steroids:
  - Steroids: 10% increase in infant endogenous cortisol level
  - Little risk to infant
  - Consider “pump and dump” for 24 hours after iv steroid course
- Postpartum IVIG as prophylaxis
  - Alternative: IVIG x 3 days at delivery, then monthly – little effect on breastfed infant (Achiron, JN 2004; Haas MSJ 2000)

Postpartum management

- Monitor for signs of post-partum depression
- Community resources and assess for social support system

Summary

- Plan for pregnancy
- Team: High risk OB, Neurologist, nursing, psychosocial support
- Treatment considerations
- Contribute to research

THANK YOU