

The Challenges of Choosing Medications in Pregnancy

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Department of Defense



Objectives

- ❖ **Help women with rheumatic disease prevent catastrophic pregnancies**
- ❖ **Prescribe anti-rheumatic medications safely during pregnancy and lactation.**





**HEALTHY
MOM**

Pregnancy
Planning

+

Pregnancy
Compatible
Medications

+

Controlled
Disease



**HEALTHY
BABY**

PLANNING

**SICK
MOM**



Lack of
Planning

+

Incompatible
or no
Medications

+

Active
Disease

**SICK
BABY**



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When a woman with SLE is not ready for pregnancy:

	Not Medically Ready	Not Personally Ready
Definition	• Taking a teratogen at conception (MMF, MTX, CYC) • Not taking needed SLE medications • Proteinuria >1g at 1st visit	• Score indicating 'ambivalent about' or 'not planning' pregnancy on validated patient survey
Impact	• 3-fold more pregnancy complications • 40% preterm delivery • 40% preeclampsia	• 2.5-fold more with emotional distress • 1/3 missing needed SLE medications

115 pregnancies in women with SLE in MADRA (2018-2023)

Harding 2024





**HEALTHY
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+

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Disease



**HEALTHY
BABY**

ACTIVITY

**SICK
MOM**



Lack of
Planning

+

Incompatible
or no
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Active
Disease

**SICK
BABY**



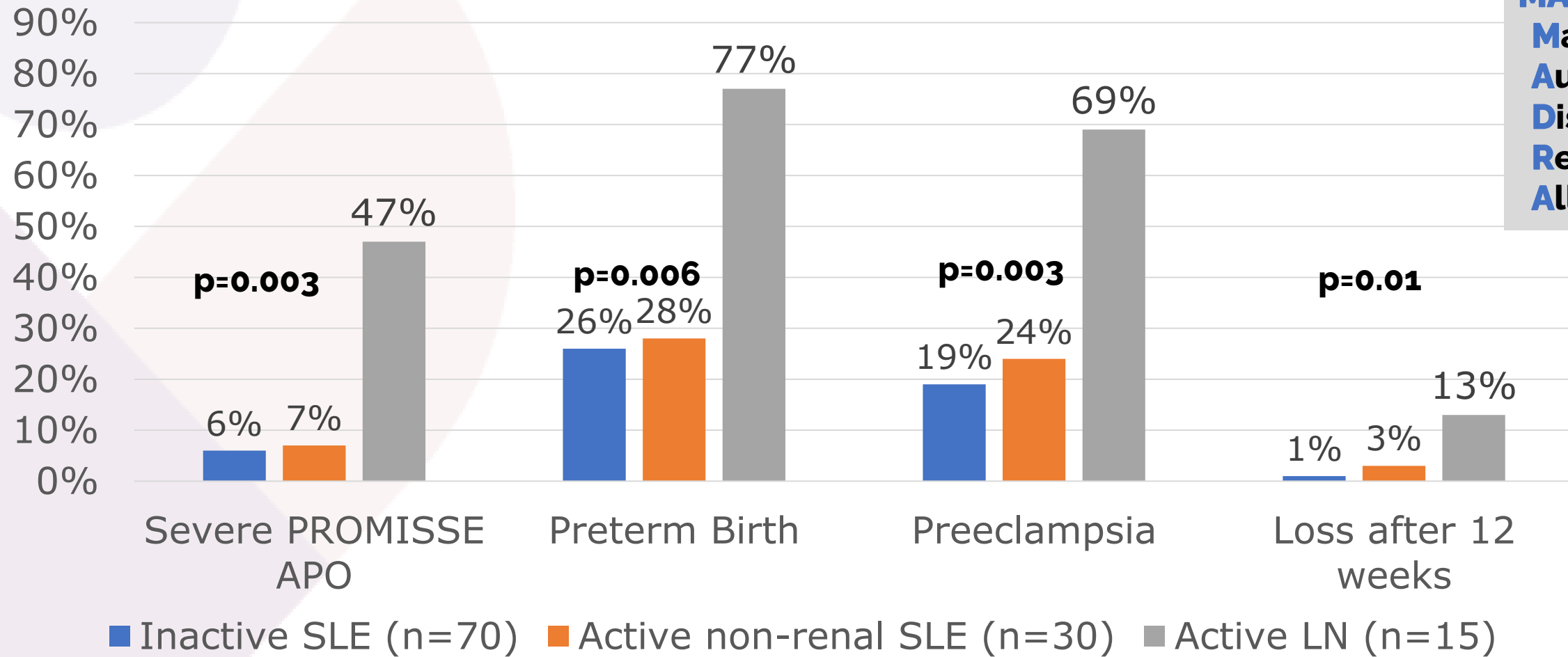
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Active
Disease

Active lupus NEPHRITIS, not non-renal activity, that causes poor outcomes

MADRA Registry
Maternal
Autoimmune
Disease
Research
Alliance



Clowse, 2023



Active
Disease

Lupus Nephritis **ACTIVITY** is the problem – inactive nephritis isn't as dangerous

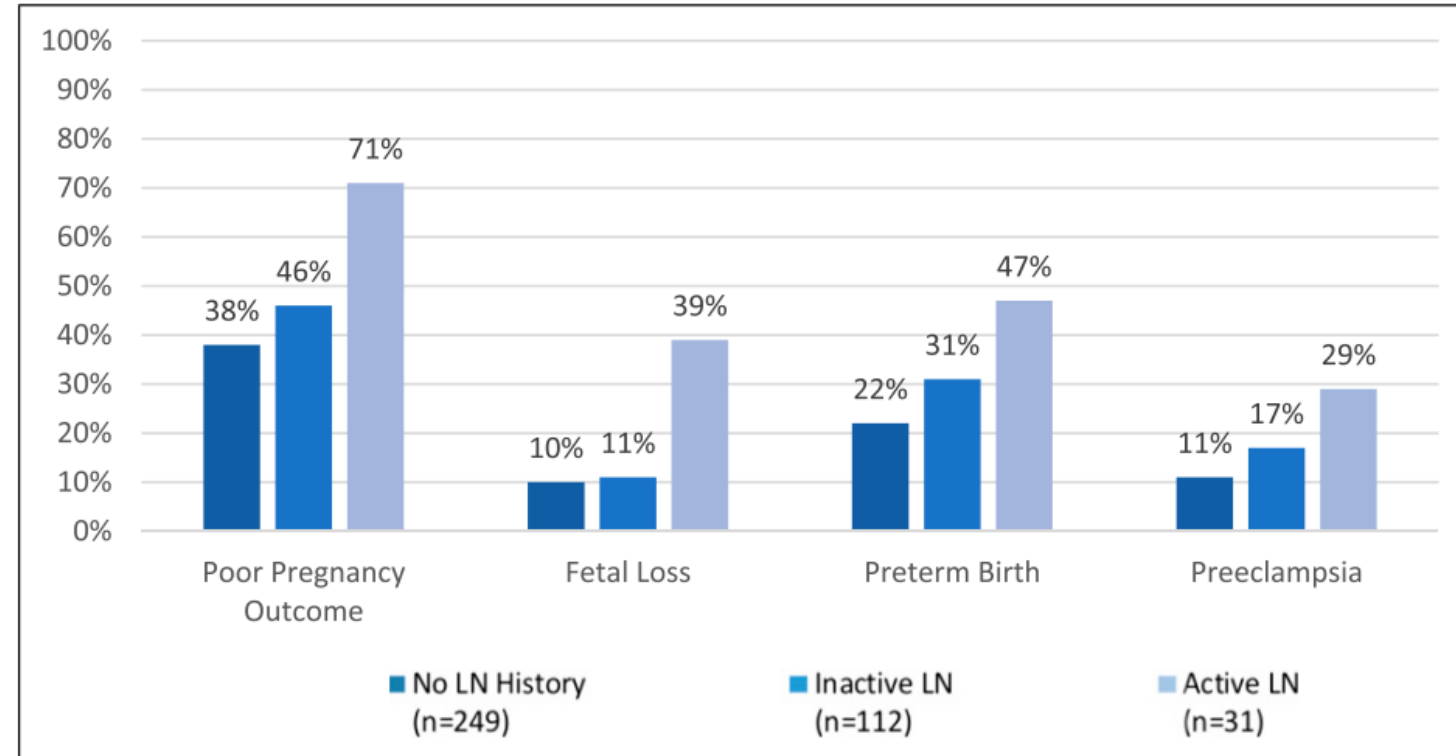
Meta-analysis of 3 prospective lupus pregnancy registries in North America

ACTIVE LUPUS NEPHRITIS in pregnancy:

- 29% had a live, term infant without preeclampsia

Women with **INACTIVE LN** :

- Outcomes fairly similar to women without LN history



Incremental increase in adverse outcomes based on lupus nephritis diagnosis and disease activity.

Active LN: history of nephritis and proteinuria ≥ 0.5 g/24 h prior to 20 weeks gestation Lucas, Lupus 2022





**HEALTHY
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+

Controlled
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**HEALTHY
BABY**

MEDICATIONS

**SICK
MOM**



Lack of
Planning

+

Incompatible
or no
Medications

+

Active
Disease

**SICK
BABY**



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Medications in Pregnancy



Medications in Pre-Conception, During Pregnancy, and Breastfeeding

Table 3. Maternal medication use: overview of medication use before and during pregnancy, and during breastfeeding

Medication	Pre-conception	During pregnancy	Breastfeeding
Conventional medications			
Hydroxychloroquine	++	++	++
Sulfasalazine	++	++	++
Colchicine	++	++	++
Azathioprine, 6-mercaptopurine	++	++	+ Low transfer
Prednisone	+ Taper to <20 mg/day by adding pregnancy-compatible immunosuppressants	+ Taper to <20 mg/day by adding pregnancy-compatible immunosuppressants	+ After a dose of >20 mg, delay breastfeeding for 4 hours
Cyclosporine, tacrolimus	+ Monitor blood pressure	+ Monitor blood pressure	+ Low transfer
Nonsteroidal antiinflammatory drugs (cyclooxygenase 2 inhibitors not preferred)	+ Discontinue if the woman is having difficulty conceiving	+ Continue in first and second trimesters; discontinue in third trimester	+ Ibuprofen preferred
Tumor necrosis factor inhibitors (tumor necrosis factor inhibitors are considered compatible with pregnancy)			
Certolizumab	++	++	++
Infliximab, etanercept, adalimumab, golimumab	+ Continue through conception	+ Continue in first and second trimesters; discontinue in third trimester several half-lives prior to delivery	++
Rituximab	+ Discontinue at conception	+ Life-/organ-threatening disease	++

Other biologics (limited safety data; limited transfer in early pregnancy but high transfer in second half of pregnancy)			
Anakinra, belimumab, abatacept, tocilizumab, secukinumab, ustekinumab	+ Discontinue at conception	X Discontinue during pregnancy	+ Expect minimal transfer due to large molecular size, but no available data
Not compatible with pregnancy			
Methotrexate	XX Stop 1–3 months prior to conception	XX Stop and give folic acid 5 mg/day	X Limited data suggest low transfer
Leflunomide	XX Cholestyramine washout if detectable levels	XX Stop and give cholestyramine washout	XX
Mycophenolate mofetil and mycophenolic acid	XX Stop >6 weeks prior to conception to assess disease stability	XX	XX
Cyclophosphamide	XX Stop 3 months prior to conception	+ Life-/organ-threatening disease in second and third trimesters	XX
Thalidomide	XX Stop 1–3 months prior to conception	XX	XX
Tofacitinib, apremilast, baricitinib	Unable to determine due to lack of data; small molecular size suggests transfer across the placenta and into breast milk		

- ++ Strongly recommend
- + Conditionally recommend
- X Conditionally recommend against
- XX Strongly recommend against



Table 2
Antirheumatic drugs in pregnancy

Drugs compatible with pregnancy		Drugs may be used if needed to effectively control maternal disease		Drugs to treat severe, refractory maternal disease, or if no alternative medication can be used		Drug to be discontinued prior to conception due to teratogenicity		Drugs that should be avoided due to insufficient data	
Drug	LoE/GoR	Drug	LoE/GoR	Drug	LoE/GoR	Drug	LoE/GoR	Drug	LoE/GoR
hydroxychloroquine (HCQ) chloroquine (CQ)	2a/B HCQ 2c/B CQ	IL12/23i: ustekinumab	2b/B	IV methylprednisolone	4/C	cyclophosphamide ⁺⁺	2a/B	apremilast	5/D
sulfasalazine	2a/B	IL-6i: tocilizumab sarilumab	4/C	IVIG	3b/C	mycophenolate ⁺⁺	2a/B	avacopan	5/D
azathioprine 6-mercaptopurine	2a/B	IL-1i: anakinra canakinumab	4/C	sildenafil	4/C	methotrexate	2a/B	JAKi: tofacitinib, baricitinib, upadacitinib, filgotinib	4/C-5/D
cyclosporine tacrolimus	2a/B CyC 2b/B TAC	IL17i: secukinumab, ixekizumab	4/C	C5i: eculizumab	4/C			bosentan	5/D
colchicine	2b/B	anti-T cell: abatacept	4/C	IL-5i: mepolizumab	4/C			leflunomide (stop 5 half-lives prior to conception or washout)	2b/B
TNFi: adalimumab certolizumab etanercept golimumab infliximab	2a/B	anti-B cell: rituximab belimumab	4/C	IL-23i: guselkumab risankizumab	5/D			voclosporin	5/D
NSAIDs ⁺ prefer ibuprofen (IBU), diclofenac (DIC); (only intermittent use, stop after 28 GW)	2a/B Ibu, Dic 2b/C COX2i			IFNAR1i: anifrolumab	5/D				
prednisone, prednisolone* (aiming at ≤ 5 mg/d)	2a/B								

anti-B cell, B-cell-targeted therapy; anti-T cell, T-cell costimulation modulator; C5i, complement protein C5 inhibitor; COX2i, cyclooxygenase 2 inhibitor; CyC, cyclosporine; GoR; grade of recommendation; GW, gestational week; ILi, interleukin inhibitor; IFNAR1i, interferon α/β receptor subunit 1 inhibitor; IV, intravenous; IVIG, intravenous immunoglobulin; JAKi, Janus kinase inhibitor; LoE, level of evidence; NSAID, nonsteroidal anti-inflammatory drug; TNFi, tumour necrosis factor.

⁺ Restrictive use recommended: can be considered if needed to control disease activity.

⁺⁺ Can be considered in severe organ- or life-threatening disease during second and third trimester: cyclophosphamide (LoE/GoR 4/C), mycophenolate (LoE/GoR 4/D).

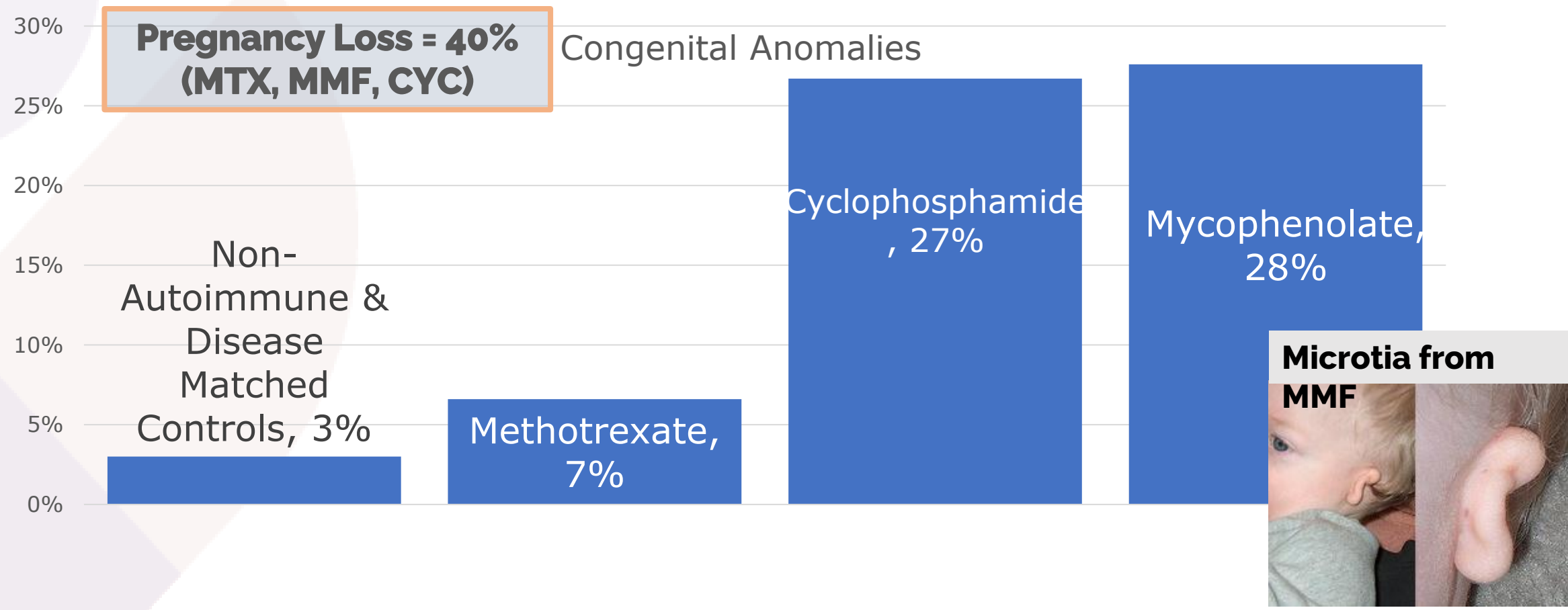


Medications that Cause Birth Defects (*teratogens*)



Incompatible
or no
Medications

Rheumatic Teratogens: Congenital Anomalies



Includes live born infants and terminated pregnancies with known fetal anomalies.

Weber-Schoendorfer. A&R 2014.
Skorpen, et al. Ann Rheum Dis 2016.
Chambers. Arthritis & Rheumatism. 2010



Incompatible
or no
Medications

Teratogens are frequently prescribed

15-30% of women of reproductive age with rheumatic disease are prescribed one of our teratogens.

Survey of US Rheumatologists 2022:
50% had cared for a patient with a teratogen exposure in pregnancy



Prescribing a teratogen:

1. Discuss birth defect risks

Use plain language

2. Ask if she's interested in getting pregnant soon.

If yes, pick another medication!

3. Ask how she is currently avoiding pregnancy.

4. Discuss contraception options, if needed.

See ReproRheum.Duke.edu or LupusPregnancy.org for more contraception information

#HIGH RISK MEDICATIONS		
	Pregnancy Loss	Birth Defects
Methotrexate	~ 40%	~ 6-10%
Mycophenolate or Cyclophosphamide	~ 40%	~ 25%
Leflunomide WITH cholestyramine washout	not increased	not increased



Pregnancy-Compatible Medications



Pregnancy-Compatible Medications

PREGNANCY COMPATIBLE

✓ GO LIST

- ✓ Hydroxychloroquine (HCQ, Plaquenil)
- ✓ Chloroquine
- ✓ Azathioprine (Imuran)
- ✓ Colchicine
- ✓ Cyclosporine (Neoral, Restasis) *[monitor blood pressure]*
- ✓ Tacrolimus (Prograf) *[monitor blood pressure]*
- ✓ Prednisone *[use sparingly]*
- ✓ TNF inhibitors
- ✓ Sulfasalazine
- ✓ IVIG



Drugs may be used if needed to effectively control maternal disease		Drugs to treat severe, refractory maternal disease, or if no alternative medication can be used	
Drug	LoE/GoR	Drug	LoE/GoR
IL12/23i: ustekinumab	2b/B	IV methylprednisolone	4/C
IL-6i: tocilizumab sarilumab	4/C	IVIG	3b/C
IL-1i: anakinra canakinumab	4/C	sildenafil	4/C
IL17i: secukinumab, ixekizumab	4/C	C5i: eculizumab	4/C
anti-T cell: abatacept	4/C	IL-5i: mepolizumab	4/C
anti-B cell: rituximab belimumab	4/C	IL-23i: guselkumab risankizumab	5/D
		IFNAR1i: anifrolumab	5/D

Medications with Insufficient Data to Clarify their Safety in Pregnancy

Drugs that should be avoided due to insufficient data	
Drug	LoE/GoR
apremilast	5/D
avacopan	5/D
JAKi: tofacitinib, baricitinib, upadacitinib, filgotinib	4/C-5/D
bosentan	5/D
leflunomide (stop 5 half-lives prior to conception or washout)	2b/B
voclosporin	5/D



My rule for drugs with insufficient info:

*If, in my clinical judgement, the woman will have **significant disease activity without the drug** that **will really negatively impact her or her baby** AND **there isn't a safer alternative**, then I lean towards continuing the drug.*



Putting this rule into action:

Active Lupus Nephritis

Does she have *significant disease activity without the drug?* **YES!**

Will that disease activity really negatively impact her or her baby? **YES!**

26 year old women with SLE since age 16 who is now 8 weeks pregnant

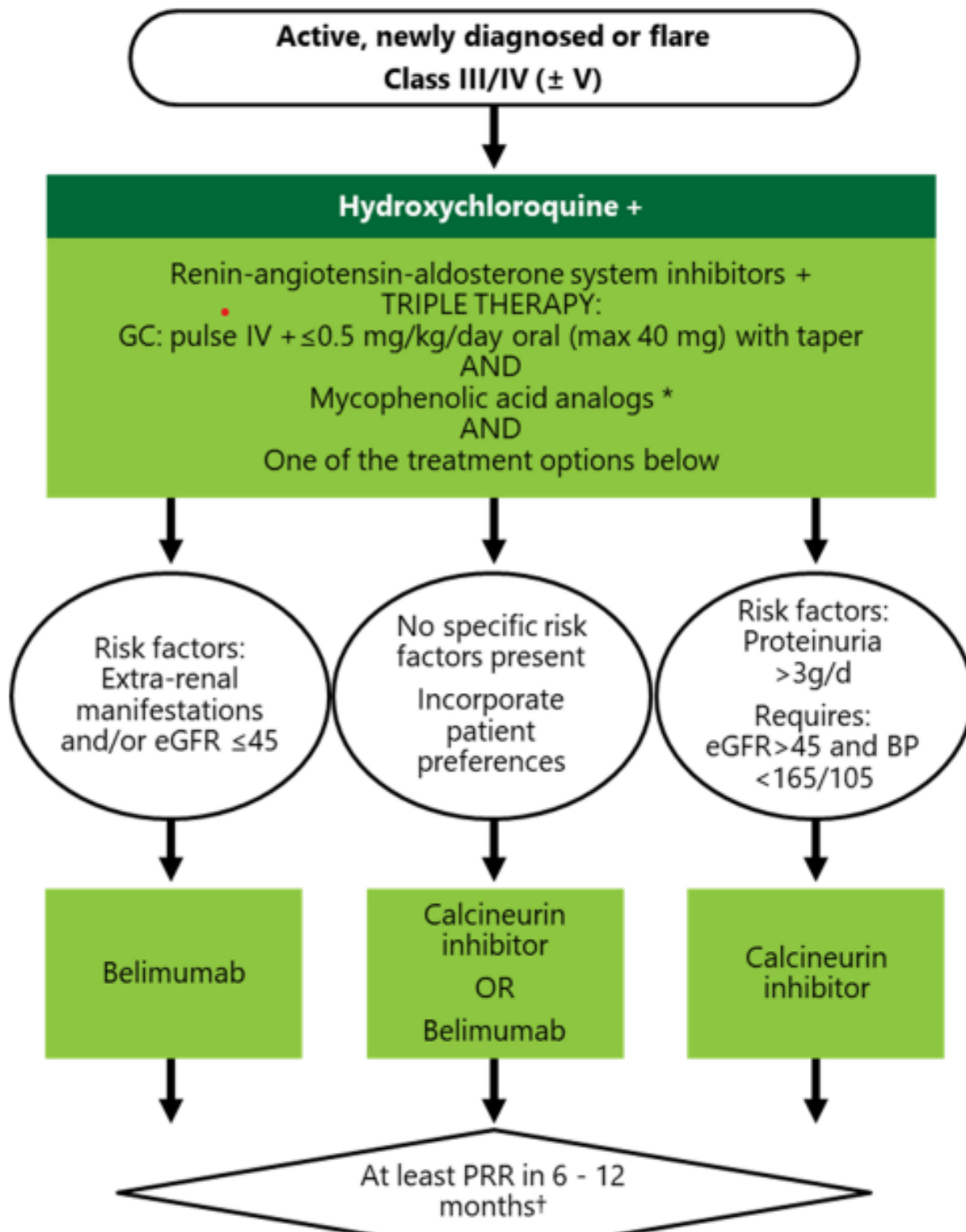
- Class IV lupus nephritis on biopsy 18 months ago
 - Mycophenolate 3g/day and prednisone
- *Off medication and out of care for the past 12 months*

Currently: she feels fine and believes her lupus is in remission

- Vitals normal (no hypertension)
- Exam normal (no edema)

Labs:

- *Urine: 2.8g on UPC, 15 WBC, 2 granular casts*
- Serum Creatinine 0.6
- Complete blood counts normal
- C3 and C4 low
- dsDNA elevated



2024 ACR Guidelines for Treatment of Lupus Nephritis

Initial treatment: 5 Drugs

- Hydroxychloroquine
- ~~ACE-inhibitor/ARB~~ Teratogen
- Steroid pulse then oral
- ~~Mycophenolate~~ Teratogen
- *Either:*
 - Belimumab Limited data
 - Calcineurin inhibitor

Are there safer options?

Our 'pregnancy-compatible' options

Azathioprine

Tacrolimus/Cyclosporin

Prednisone



What about other medications?

Obinutuzumab or Rituximab

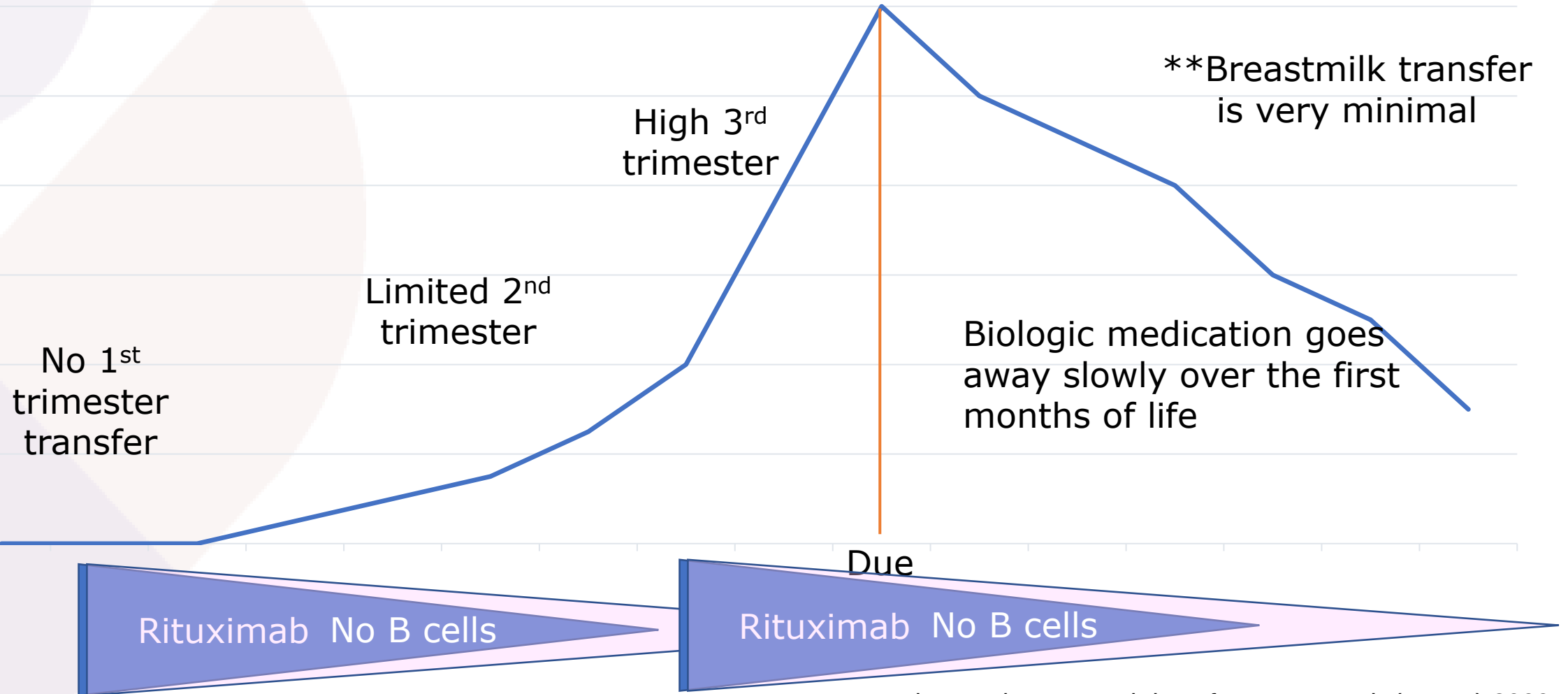
Belimumab

Voclosporin



Baby antibody (biologic medication) exposure

Term Infant: 160% of maternal antibody concentration



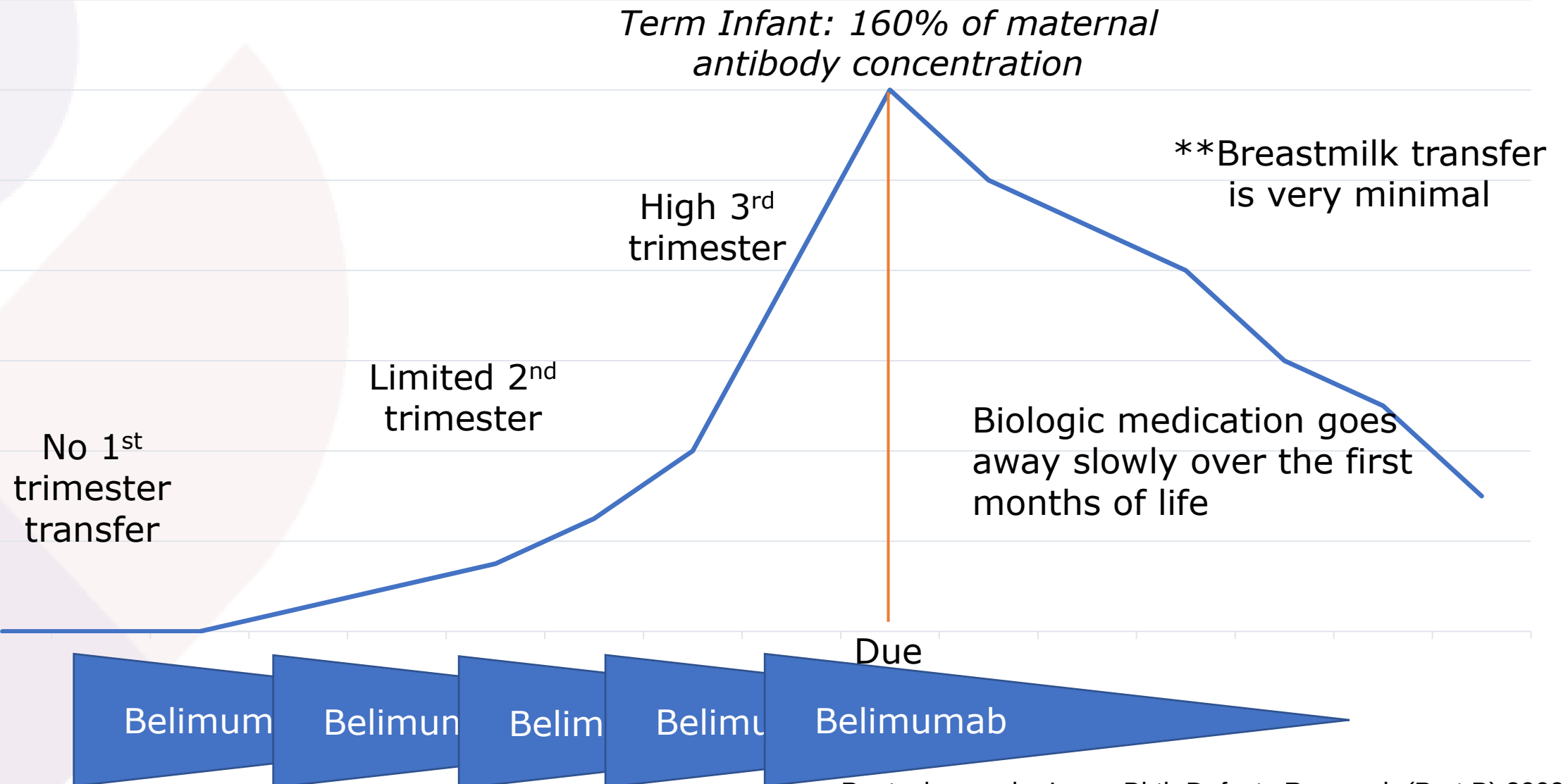
Pentsuk, van der Laan. Birth Defects Research (Part B) 2009



Obinutuzumab & Rituximab

- Limited 1st trimester transfer, so unlikely to cause birth defects
- High transfer later in pregnancy, so likely for the baby to have no B cells at delivery
 - *Infant vaccinations ineffective in the first 6-12 months?*
 - *Increased risk for infections?*
- Best selling points:
 - 1-2 infusions gets months of effect
 - Adherence
- Worst selling points:
 - Rituximab: Random. trial: didn't help lupus nephritis with MMF
 - Obinutuzumab: Not a lot of data; unclear how quickly it helps.

Baby antibody (biologic medication) exposure



Pentsuk, van der Laan. Birth Defects Research (Part B) 2009



Belimumab

- Limited 1st trimester transfer, so unlikely to cause birth defects
 - High transfer later in pregnancy, so likely for the baby to have low B cell function after delivery
 - Does this matter?
 - Repeated dosing – monthly or weekly
 - Continue all pregnancy? Stop at some point?
 - Slow impact on proteinuria
- 

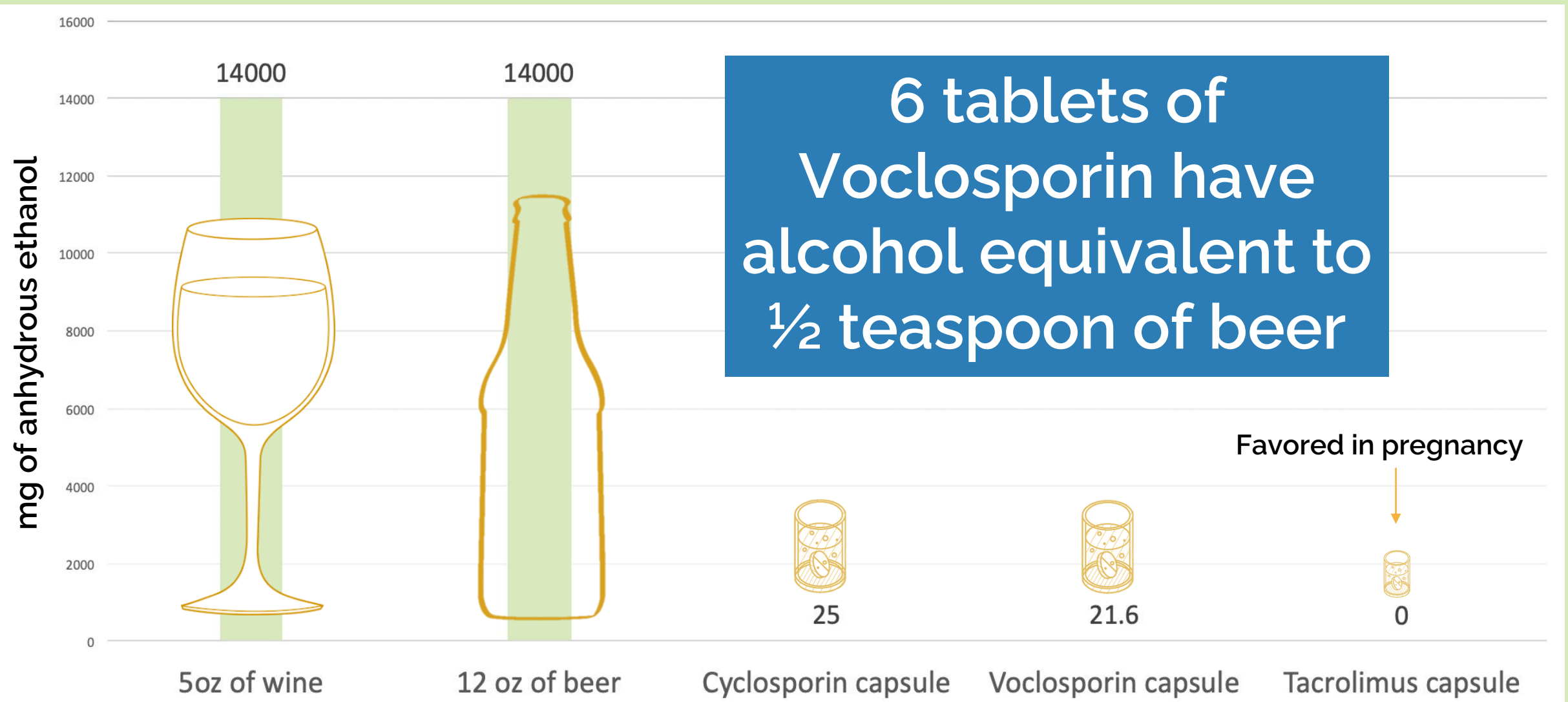
Belimumab Pregnancy Outcomes	Clinical trials		Belimumab Pregnancy Registry		Spontaneous reports
	Belimumab + ST	Placebo + ST	Belimumab + ST, prospective	Belimumab + ST, retrospective	Belimumab + ST
- Mostly 1st trimester exposure - Very few continued drug					
Total number of pregnancies	181 [§]	28	57	10	310
Pregnancies with known outcomes (n=303) (excluding elective terminations)					
Pregnancy loss	This data is <i>MESSY</i>. <i>Likely not a major teratogen.</i> - <i>Not as bad as MMF.</i> - <i>Unclear if NO risk.</i>				
<u>BIRTH DEFECTS:</u>					
Pregnancy loss with birth defect	0	1/7 (14.3%)	0	0	2/43 (4.7%)
Live infants with birth defect	4/72 (5.6%)	0/9	10/46 (21.7%)	0/4	1/92 (1.1%)
1/14 in trials/BPR on MTX, 1/14 ACE-I					

Voclosporin

- Calcineurin Inhibitor: Similar to tacrolimus/cyclosporin in action
- Best selling point:
 - Rapid decrease in proteinuria
 - Dosing is more reliable
- Worst selling point:
 - A lot of pills every day
 - Alcohol in the tablet → loud warnings from the FDA and the company to avoid in pregnancy

Voclosporin and alcohol

- “There is no known safe level of alcohol in pregnancy.”
- But there is known unsafe level of lupus nephritis in pregnancy!!



https://www.ema.europa.eu/en/documents/product-information/lupkynis-epar-product-information_en.pdf

Slide made by Sara Sheikh. MD – permission granted for use



Efficacy and safety of voclosporin versus placebo for lupus nephritis (AURORA 1): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial

Brad H Rovin, Y K Onno Teng, Ellen M Ginzler, Cristina Arriens, Dawn J Caster, Juanita Romero-Diaz, Keisha Gibson, Joshua Kaplan, Laura Lisk, Sandra Navarra, Samir V Parikh, Simrat Randhawa, Neil Solomons, Robert B Huizinga

Lancet 2021; 397: 2070–80

MMF + steroid taper

Voclosporin

Placebo

N=179

N=178

Time to 50% reduction in UPC

29 days

65 days

Complete Renal Response (24wks)

32%

20%

Partial Renal Response (24wks)

70%

50%

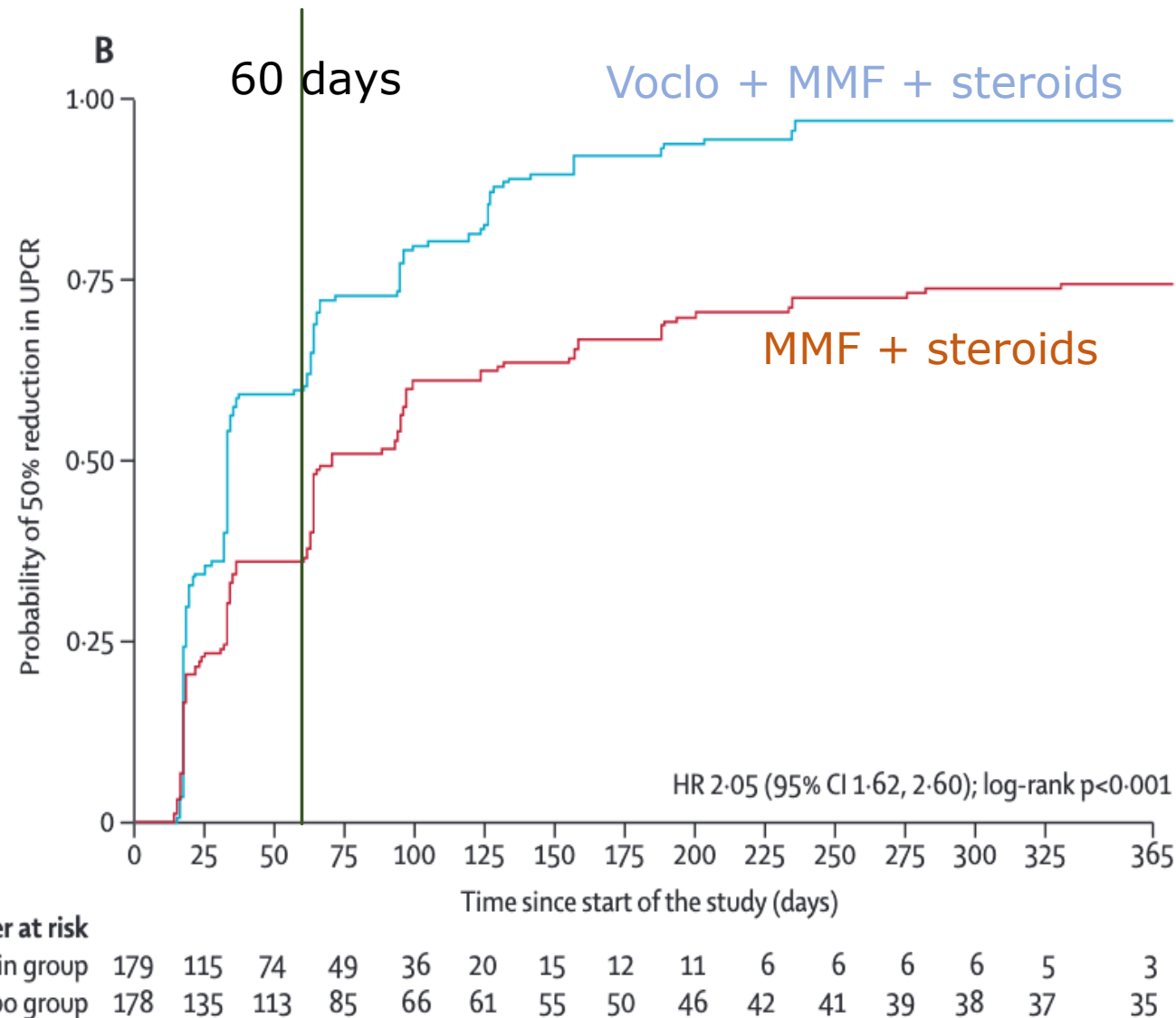


Figure 3: Probability of UPCR of ≤ 0.5 mg/mg (A) and of $\geq 50\%$ reduction from baseline in UPCR (B; intention-to-treat population)

Putting my rule into action: Active Lupus Nephritis

- *If, in my clinical judgement, the woman will have **significant disease activity without the drug** **YES!***
- *that will really negatively impact her or her baby **YES!***
- *AND there isn't a safer alternative **YES!***
- *Then **I lean towards continuing (or starting) the drug.***

Options:

- *HQC, AZA, prednisone*
- *AND ADD: Tacrolimus, Obinutuzumab, or Voclosporin*



Inflammatory Arthritis



Pregnancy-Compatible Medications for Inflammatory Arthritis

PREGNANCY-COMPATIBLE MEDICATIONS:

These medications are also compatible with breastfeeding.

- **TNF-inhibitors**
- **Hydroxychloroquine** (or Chloroquine)
- **Sulfasalazine** (with 2mg folic acid each day)
- **Azathioprine**
- **Steroid joint injection**
- **Prednisone** (use sparingly for flares)
- **NSAIDs** - discuss with your OB



TNF-INHIBITORS:

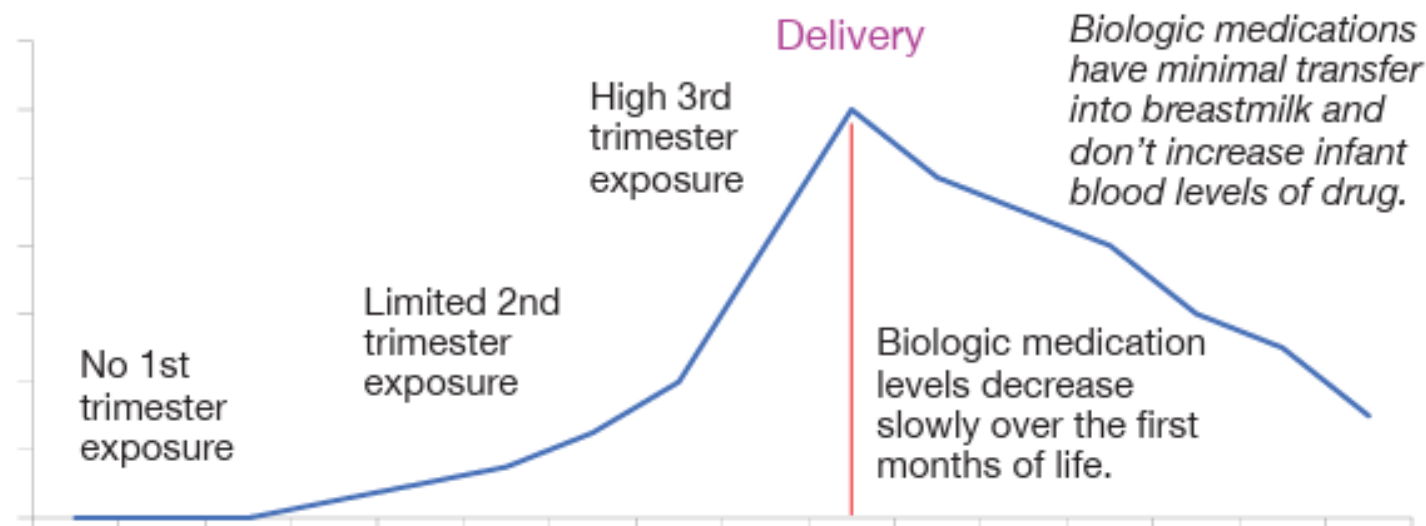
Certolizumab (Cimzia®) does not cross the placenta and can be continued throughout pregnancy.

Adalimumab (Humira®)
Infliximab (Remicade®)
Etanercept (Enbrel®)
Golimumab (Simponi®)

Cross the placenta in the 2nd half of pregnancy. Consider holding for the last 1-2 months of pregnancy to limit transfer to the baby

BIOLOGIC MEDICATION EXPOSURE:

Infant exposure to the mother's biologic medications



Putting my rule into action:

Severe Inflammatory Arthritis

26 year old women with JIA since age 16 who is now 8 weeks pregnant

- Positive Rheumatoid factor and CCP antibody
- Erosions, deformities, and limited range of motion:
 - wrists, elbows, ankles
- *Tocilizumab alone for the past year*

Currently: she feels fine and believes her JIA is in remission

- Vitals normal
- Exam: joint deformities as above but no synovitis and no tenderness with palpation or range of motion

Labs:

- CRP 0.06 (normal)
- Serum Creatinine 0.6
- Complete blood counts normal

Does she have **significant disease activity without the drug?** **YES!**

Will that disease activity really negatively impact her or her baby? **It might.**

Severe Inflammatory Arthritis in Pregnancy

Impact on the Woman

- Risk for significant flare off medication
 - Stop TNF: 63% flare
 - Continue TNF: ~20% flare
 - Long-term damage & disability
- Limits fertility

Pregnancy may improve arthritis, but not as much as modern medications!

Impact on pregnancy/baby

- No increase in pregnancy loss
- Preterm birth:
 - Inactive RA: <10% preterm
 - Active RA: ~25% preterm
 - Typically 34-36wks
- Risks from maternal medications
 - Birth defects: methotrexate
 - Immunosuppression: biologics dosed near term

Tocilizumab (Actemra®)

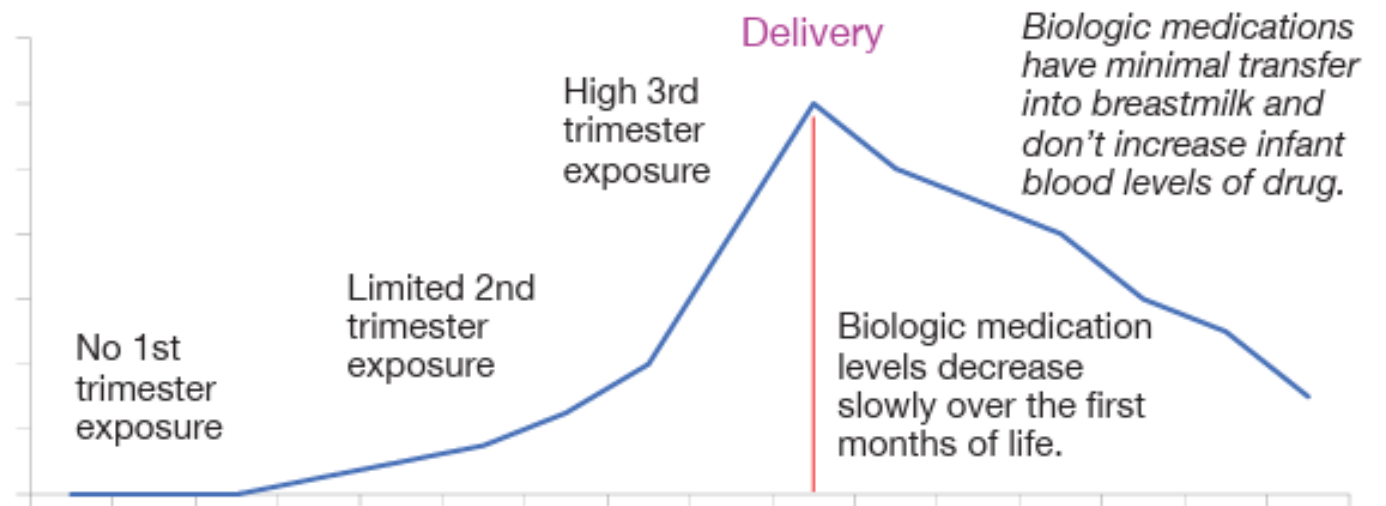
Anti-IL-6 receptor **IgG1** antibody

SQ: every other week

IV: every 4 weeks

Main side effects:

- Infection
- Dyslipidemia (mild)



Tocilizumab: what pregnancy data do we have?

180 Prospective Pregnancies

- 22% spontaneous abortions
- 17% elective terminations
- 1 stillbirth
- 4.5% malformations
- 31% preterm births

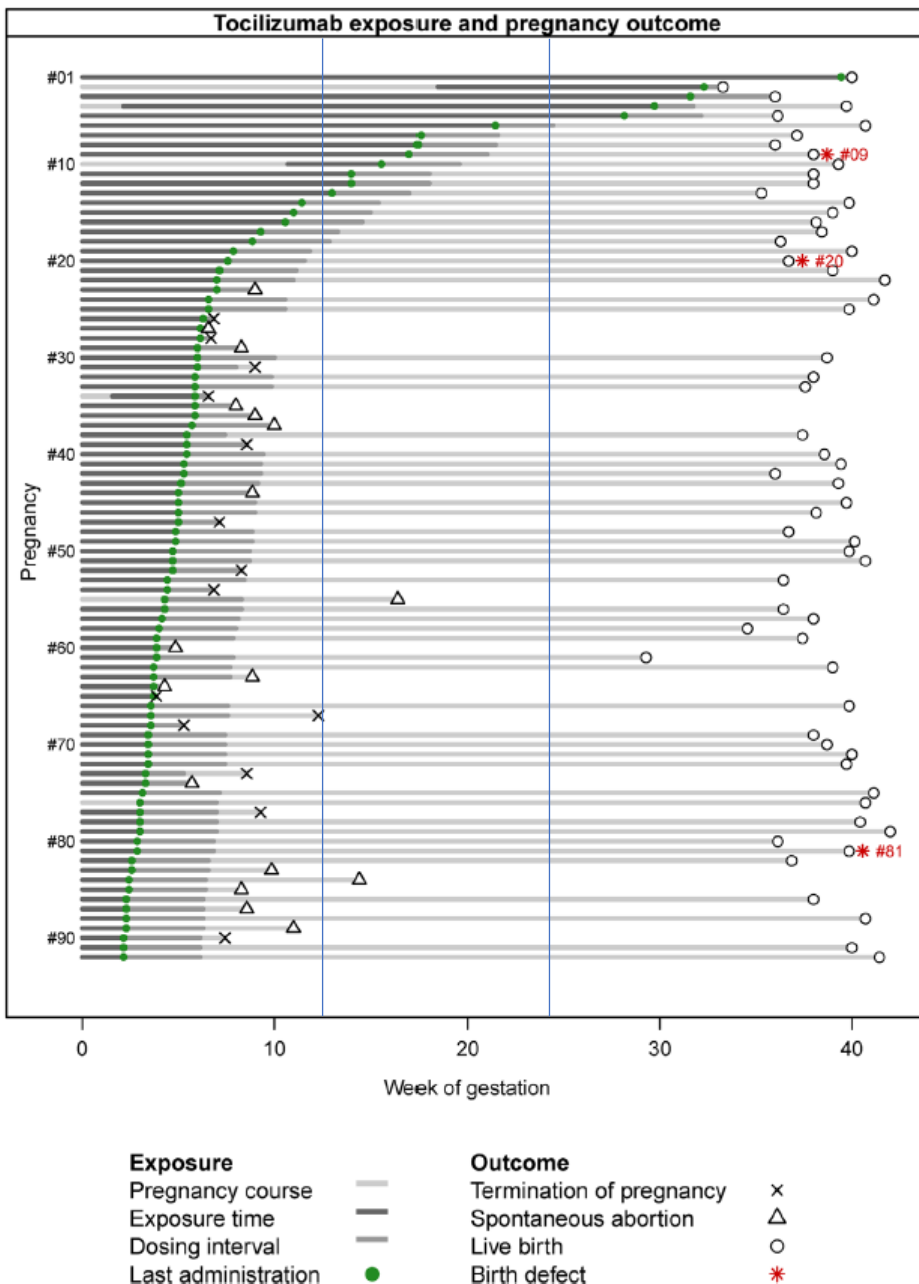
~10 women continued toci through pregnancy

Hoeltzenbein. Seminars in Arthritis. 2016

25 pregnant women treated with IL-6i for severe COVID-19:

- 9 in 2nd trimester; 16 in 3rd trimester
- 16 delivered preterm
- transient neonatal cytopenia in 6/19 tested – may be due to prematurity.

Nana 2024



Tocilizumab placental transfer *lower* than expected?

Takayasu's Arteritis & AOSD: continued tocilizumab through pregnancy

Tocilizumab concentration at Delivery:

- Maternal serum: 13,304 ng/mL
- Umbilical cord blood: 1,009 ng/mL

8% of maternal level

Breastmilk: 5 measurements

- TCZ milk:mother serum at delivery: **1:2000**

Moriyama. Scand J Rheum 2020

Tocilizumab concentration at Delivery:

- Maternal serum: 4893 ng/mL
- Umbilical cord blood: 683 ng/mL

14% of maternal level

• Infant serum:

- Day 5 of life: 176 ng/ml
26% of level at birth
- Day 28 & 55 of life: *none*

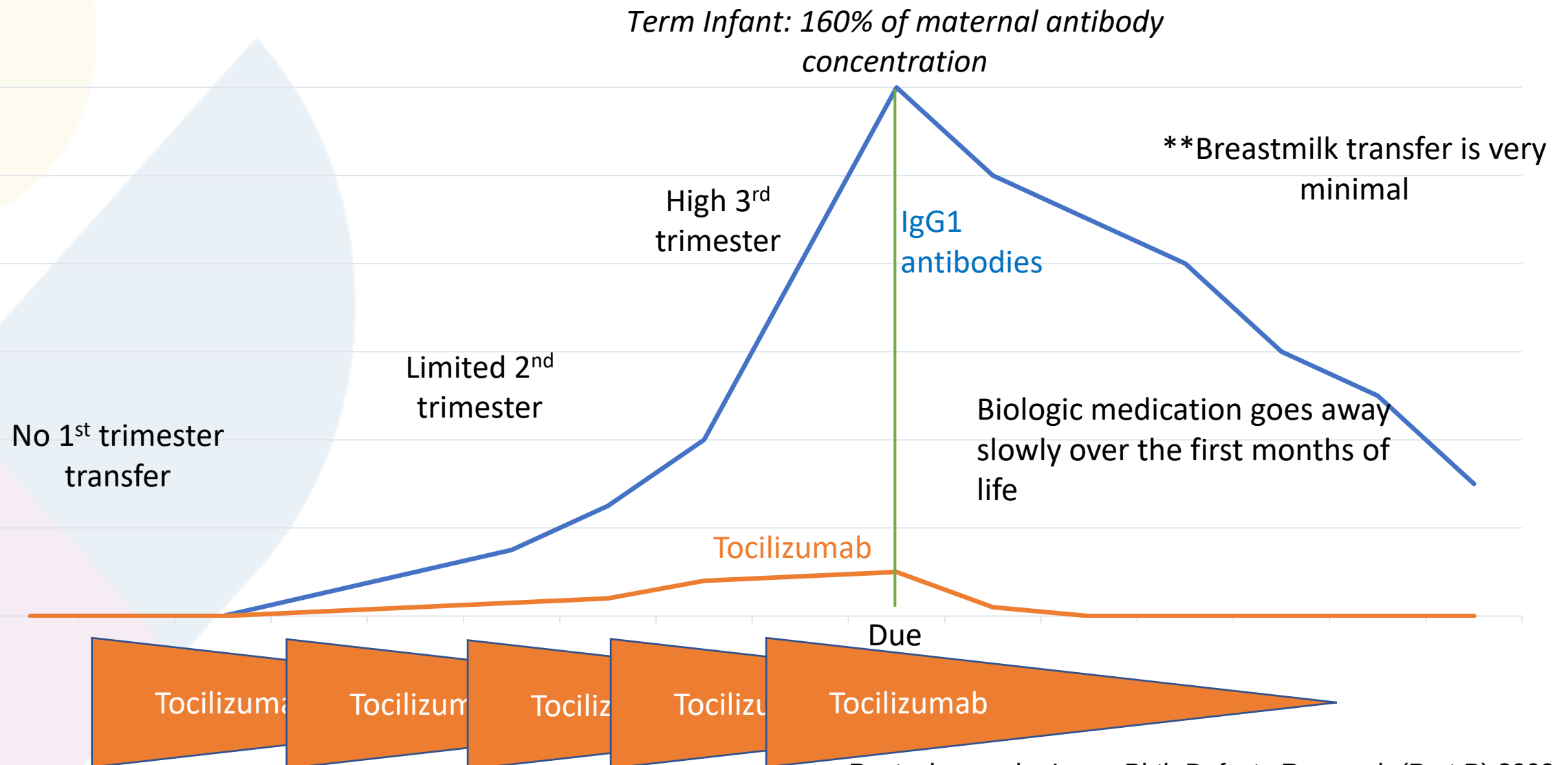
Breastmilk:

- Serum max (day of dosing): 43,001 ng/ml
- Milk max (4 days after dosing): 205 ng/ml

(0.5% of serum level)

Saito. Rheumatology 2019

Possible Tocilizumab exposure



Moriyama. Scand J Rheum 2020 Saito. Rheumatology 2019

Pentsuk, van der Lann. Birth Defects Research (Part B) 2009



Putting this rule into action: Active Inflammatory Arthritis

- *If, in my clinical judgement, the woman will have **significant disease activity without the drug** **YES!***
- *that will really negatively impact her or her baby **Sort of***
- *AND there isn't a safer alternative **Maybe?***
- *Then **I lean AWAY FROM continuing the drug.***

Options:

- *TNF-inhibitor – try her favorite or a new one*
- *HCQ, SSZ*
- *If this doesn't work, then I'd consider Tocilizumab.*



Lactation

“For the first 6 months I flared while breast feeding and... I would have my spouse hold the baby up to my breasts (to) breast feed. I was in bed for 6 months.”



// ANGELA BURZO/INSTAGRAM



**Women DO NOT need to choose between treating their
rheumatic disease and breastfeeding their baby.**
95% of women can safely do both



BREASTFEEDING:

Compatible Medications

- All pregnancy-compatible medications
- All biologics, including all TNF-inhibitors and newer injectable or IV medications
- Methotrexate can be considered if breastmilk is dumped in the 24 hours after the weekly dose

Avoid

- Mycophenolate and cyclophosphamide
- New oral small molecule medications, including tofacitinib, baricitinib, apremilast, and others

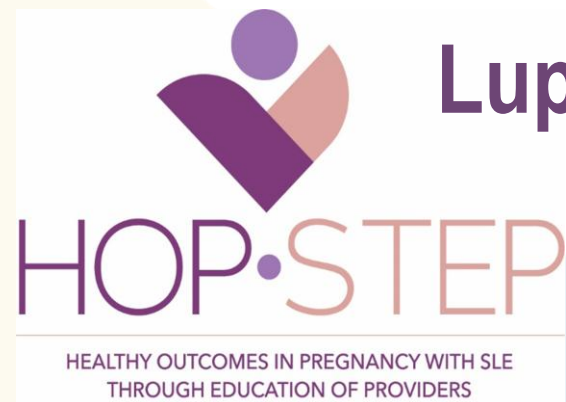


Take Home Points

- ❖ The key to rheumatic pregnancy success is **TIMING**
 - ❖ *THIS TAKES ACTIVE PLANNING!*
- ❖ Weigh the risks to the mother & infant from **DISEASE FLARE vs MEDICATION**
 - ❖ **High flare** risk that harms mother/baby: give the **drug with limited data**
 - ❖ **Low flare** risk or **limited harm** to mother/baby: **drugs with some data**
- ❖ See the **LupusPregnancy.org & ReproRheum.Duke.edu Discussion Guides & website** to guide accurate conversations about pregnancy planning

Get to the Joint Goal:
Having the safest pregnancy possible!





LupusPregnancy.org

Preparing for Pregnancy: A Checklist for Patients & Providers



ReproRheum.duke.edu

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CONTRACEPTION

