RhAPP

RHEUMATOLOGY ADVANCED PRACTICE PROVIDERS

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Pre-Conception and Pregnancy

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Disclaimer

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Faculty Disclosure

- **Jonna Zelie, PA-C:**
  - No disclosures to report

- **Jessica Farrell, PharmD**
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Objectives

- Discuss pre-conception planning and risk for patients with rheumatic disease
- Evaluate safe and effective therapeutic options for rheumatic disease in pregnant patients
- Review safety data associated with medications used for rheumatic disease in preconception and pregnancy
- Discuss treatment options compatible during lacation

Pregnancy in Rheumatic disease

- Many rheumatic diseases affect women of childbearing age
  - Fertility is usually unaffected
- Response of rheumatic diseases depends on many different factors
  - Disease extent/activity/severity
  - Presence of autoantibodies
  - Co-morbidities
- High risk pregnancy
  - Defined as when either the mother and/or developing fetus are at an increased risk of complications during pregnancy, delivery or post-partum
  - Contributing Factors
    - Advanced Age
    - Underlying disease states/medical history
    - Multiple pregnancy

Soh MC et al. Rheumatology. 2014; 54(3):572-587.

Pregnancy considerations

- Disease activity during preconception phase
- Type of rheumatic disease
  - Presence of antibodies
  - Overlap disease
- Higher incidence of spontaneous abortions, preterm deliveries , stillbirths, and low birth weights at delivery
- Comorbidities
- Preconception planning

De Carolis S, et al. Autoimmun Rev.2013;13(2):103-107.
Soh MC et al. Rheumatology. 2014; 54(3):572-587

Set a plan…

Discuss goals for family planning with any patient establishing care for a new diagnosis as well as regularly during follow up visits.

If contemplating pregnancy, start planning as soon as possible and encourage open conversations with your patients.

Weigh your options.

Table 1. Safety and efficacy of various contraceptive methods in women with RMD*

Method	Safety in women with RMD	1-year failure rate, %†
Highly effective (LARC)		
Copper IUD	Safe in all women with RMD; may increase menstrual bleeding	<1
Progestin IUD	Safe in all women with RMD; may decrease menstrual bleeding	<1
Progestin implant	Limited data, but likely safe in all women with RMD	<1
Effective		
Progestin-only pill (daily)	Safe in all women with RMD; higher rate of breakthrough bleeding than with combined contraceptives; must take same time every day for efficacy	5–8
DMPA (IM injection every 12 weeks)	Safe in most women with RMD; exceptions: positive aPL, at high risk for OP	3
Combined estrogen and progesterone pill (daily)	Safe in most women with RMD; exceptions: positive aPL, very active SLE	5–8
Transdermal patch (weekly)	Safe in most women with RMD; exceptions: positive aPL, SLE; serum estrogen levels higher than with pill or vaginal ring	5–8
Vaginal ring (monthly)	Safe in most women with RMD; exceptions: positive aPL, very active SLE	5–8
Less effective		
Diaphragm	Safe in all women with RMD	12
Condom	Safe in all women with RMD; only form to prevent STD	18
Fertility awareness–based methods‡	Safe in all women with RMD; limited efficacy, especially if menses are irregular	24
Spermicide	Safe in all women with RMD; use with condoms or diaphragm to improve efficacy	28

* RMD = rheumatic and musculoskeletal disease; LARC = long-acting reversible contraception; IUD = intrauterine device; DMPA = depot medroxyprogesterone acetate; IM = intramuscular; aPL = antiphospholipid antibody; OP = osteoporosis; SLE = systemic lupus erythematosus; STD = sexually transmitted disease.
† Percent of women who will become pregnant within the first year of typical use.
‡ Methods based on the timing of the menstrual cycle.

Soammaritano, et al. Arthritis Rheumatol,(2020): 529-556

Emergency Contraception

Risks of emergency contraception are low compared to those of unplanned pregnancy.

Levonorgestrel (Plan-B) has no medical contraindications to use

In high-risk situations (severe renal disease, patients with cardiomyopathy, PAH), the option of therapeutic termination of pregnancy may be lifesaving and should be discussed with the patient

Soammaritano, et al. Arthritis Rheumatol,(2020): 529-556

Pregnancy in Lupus

- Continue HCQ if possible
- Consider low dose aspirin (81mg)
- Screen for anti-phospholipid antibodies

Soammaritano, et al. Arthritis Rheumatol,(2020): 529-556

Pregnancy Counseling and Considerations

- Clinical antiphospholipid syndrome defined as:
  - History of venous or arterial thromboembolism
  - Obstetric complications and no venous or arterial TE
- When clinical antiphospholipid syndrome is present:
  - Full anticoagulation therapy with LMWH or unfractionated heparin is advised
- If pregnant woman has positive antiphospholipid syndrome antibodies and prior late-stage fetal loss or recurrent 1st trimester miscarriages:
  - Prophylactic LMWH or unfractionated heparin during pregnancy (unfractionated heparin if near term) and 6 weeks postpartum
- Co-management by a hematologist, an obstetrician, and rheumatology provider is advised for management of these patients

Sammaritano LR, et al. 2020 Apr;72(4):529-556.

RA and Pregnancy

75% women experienced improvement in their RA symptoms during pregnancy

90% relapsed within 3 months of delivery

Barrett et al demonstrated 16% remission by 3rd trimester

Risk vs Benefit?

Mitchell K et al. Scand J Rheumatol 2010;39:99–108.
Vinet E et al. Expert Review of Clinical Immunology 2009;5(1)27.

Paternal exposure

- Agents that may cause azoospermia
  - Cyclophosphamide
  - MTX (prospective data supports no adverse effect on pregnancy outcomes)
  - Colchicine (possible)
  - Sulfasalazine

- Biologics
  - Likely safe

Soammaritano, et al. Arthritis Rheumatol,(2020): 529-556

Lactation and Breastfeeding

- Many variables exist in regards to drug excretion in lactation
- Lactmed is a NIH resource with information on the use of medications in breastfeeding
- TNF inhibitors are minimally excreted in breast milk and are likely destroyed in an infant's GI tract
- Certolizumab has been shown to have lower blood concentration in breastfeeding infants versus in utero
  - Case report of one woman's infant had a certolizumab cord blood level of 1.02 mg/L at birth and 0.84 mg/L when breastfeeding seven days after the mother received an injection

LactMed. Available at: https://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm

csDMARDs & Pregnancy

Drug	Recommendations on its use in pregnancy	Breast-feeding
Methotrexate	**Reliable contraception advised.** **Discontinue at least 3 months prior to pregnancy** with daily high-dose folic acid supplementation. Exposed fetuses should be scanned as early as possible (at 16 weeks gestation) to determine whether there are any congenital anomalies to facilitate elective termination if the mother wishes.	**X**
Leflunomide	**Reliable contraception advised.** Washout with cholestyramine 8 g three times per day for 11 days repeat until drug concentrations are <0.03 mg/ml taken 2 weeks apart. If exposed in early pregnancy, offer washout and reassure the woman that birth outcomes of exposed women are no different from disease-matched controls.	**X**
Azathioprine	**Continue in pregnancy and lactation**[a]	√
Mycophenolate mofetil	**Reliable contraception advised.** **Discontinue for at least 3 months prior to pregnancy.**	**X**

√: safe for breastfeeding; X: unsafe or not recommended for breastfeeding

Adapted from Soh MC et al. Rheumatology 2015;54:572-587
Sammaritano LR et al. Arthritis Rheumatol. 2020 Apr;72(4):529-556.

Biologics and Pregnancy

Drug	Effects on Organogenesis	Effects on fetus/neonate	Breast-feeding	Recommendations on its use in pregnancy
Etanercept	Animal studies are reassuring. Some centers for assisted reproduction are using it for the treatment of immune-mediated recurrent miscarriages.	Active transplacentral transfer of anti-TNF agents with a risk of neonatal immune suppression if drugs are continued throughout pregnancy.	√	Continue until 32 weeks gestation[a]
Infliximab			√	Continue until 21 weeks[a]
Adalimumab			√	Continue until 28 weeks, although evidence is lacking due to difficulty in getting commercially available tests for drug levels[a]
Cetolizumab pegol	None known	Negligible transplacental transfer	√	Due to very low levels in cord blood, safe to continue in pregnancy.
Abatacept	Unknown; available data in combination with MTX exposure, high rate of miscarriage	Unknown	?	Due to limited data alternative therapy should be used during pregnancy and lactation
Tocilizumab	Unknown; available data in combination with MTX exposure, high rate of miscarriage	Unknown	?	Due to limited data alternative therapy should be used during pregnancy and lactation
Rituximab	None known	Transient cytopenias and neonatal B cell depression. Did not affect the efficacy of vaccination.	√	Attempt to discontinue 12 weeks prior to delivery if at all possible to prevent neonatal B cell depression.

[a]If given beyond the recommended gestation, the neonate should not receive any live vaccines for the first 6 months of life. The two live vaccines commonly given in the neonatal period are BCG and the rotavirus vaccine. √: safe for breastfeeding; X: unsafe or not recommended for breastfeeding

Adapted from Soh MC et al. Rheumatology 2015;54:572-587;
Levy et al. Autoimmunity Reviews 2016;15:955-963

Biologics Use in SLE and Pregnancy

Drug	Recommendations on its use in pregnancy	Breast-feeding
Belimumab	Based on limited information, use of belimumab may be continued through conception in women with rheumatic and musculoskeletal diseases who are planning a pregnancy and not able to use alternative therapies; use should be discontinued once pregnancy is confirmed. Conception should be planned during a period of quiescent/low disease activity	?/√
Rituximab	Attempt to discontinue 12 weeks prior to delivery if at all possible to prevent neonatal B cell depression.[a]	√

√: safe for breastfeeding; X: unsafe or not recommended for breastfeeding

Soh MC et al. Rheumatology 2015;54:572-587;
Levy et al. Autoimmunity Reviews 2016;15:955-963
Sammaritano LR et al. Arthritis Rheumatol. 2020 Apr;72(4):529-556
Gotestam Skorpen C et a. Ann Rheum Dis 2016;75:795–810.

Biologics and Pregnancy Summary

- “Disease activity at time of conception and during pregnancy may be associated with a risk of low birth weight, premature births, and spontaneous abortions.”
- Biologic exposure may be associated with congenital malformations
- Overall risk of exposure is relatively low
- Emerging registry data becoming available
- Reassure women with accidental pregnancies
- Discontinue monoclonal antibodies before gestational week 30

Bogas M et al. Acta Rheumatol Port. 2011;36(3):219-232
Soh MC et al. Rheumatology 2015;54:572-587

The Pharmacist's Role

- Assess risk vs benefit
- Selecting the right biologic based on available safety data
- Informing the patient of potential risks and side effects
- Addressing specific patient concerns
- Navigating treatment of adverse events precipitated by TNF Inhibitor therapy
- Staying up to date on the most recent data

Meet Kayla

- 35-year-old female with systemic lupus erythematosus (SLE) (diagnosed 6 years a
currently flaring after an afternoon outside at a family picnic.
- She presents with thrombocytopenia, anemia and rash (burning, pruritus).
- She has 3+ protein and 2+ blood in the urine and presents with active lupus nephritis.
- Her most recent labs are hemoglobin (9.8 g/dL), hematocrit (29.8%) and platelets (31,000 cells/mm3).
- She is currently treated with belimumab (Benlysta) and hydroxychloroquine (HCQ). To treat the flare, she was started on prednisone 60 mg daily and will be starting rituximab (Rituxan) in place of belimumab. She refused to start treatment with mycophenolate mofetil.
- It was recommended that as needed rituximab dosing schedule be utilized until low disease activity is achieved and transition back to belimumab for maintenance therapy.
- Aimee is considering another pregnancy but realizes she needs to wait until her disease is stable. She is a mother to a healthy 2-year-old, and her last pregnancy went well. She was controlled on HCQ 200 mg BID during her pregnancy.

Back to Kayla: 2 Months Later

- **35-year-old female with systemic lupus erythematosus (SLE)** (diagnosed 6 years ago) currently recovering from a lupus nephritis flare.
- She is currently receiving hydroxychloroquine (HCQ) and prednisone 10 mg daily.
- She received 1 cycle of rituximab (2 months ago).
- Her rheumatologist is considering re-starting her belimumab.
- Aimee is considering another pregnancy but realizes she needs to wait until her disease is stable. She is mother to a healthy 2-year-old, and her last pregnancy went well. She was controlled on HCQ 200 mg BID during her pregnancy.