



# RhAPP

RHEUMATOLOGY ADVANCED  
PRACTICE PROVIDERS

## Inaugural National Conference

**December 3 – 5, 2020**

VIRTUAL CONFERENCE



**RhAPP**

RHEUMATOLOGY ADVANCED  
PRACTICE PROVIDERS

# Managing the Pregnant Patient

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Clinic

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# Faculty Disclosures

- Tara Kennedy, FNP-BC:

There are no disclosures at this time.



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# Managing the Pregnant Patient

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# Objectives

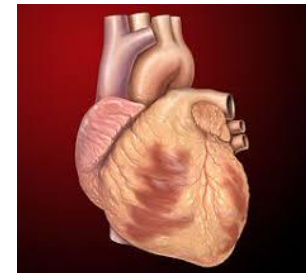
- Review hematologic and immunologic changes that occur during pregnancy
- Identify potential perinatal complications associated with rheumatic and musculoskeletal disease
- Review medications safe to use in pregnancy and those to avoid
- Identify safe and effective contraceptive methods in women with rheumatic and musculoskeletal disease

# Cardiovascular Changes

**Table 1 | Summary of cardiovascular changes during pregnancy.**

Variable	Change
Cardiac output	Increased by 30–50%
Stroke volume	Increases to a maximum of 85 mL at 20 weeks of gestation
Heart rate	Increased (approaches 90–100 beats/minute at rest during the third trimester)
Systemic vascular resistances	Decrease 21% (nadir at 20–24 weeks)
Pulmonary vascular resistances	Decrease by 34%
Pulmonary capillary wedge pressure	No significant change
Colloid osmotic pressure	Decreased by 14%
Hemoglobin concentration	Decreased

7-8 liter increase blood volume



# Changes in plasma volume

- Begins as early as 6 weeks
- Improved transport of nutrients and extraction of waste
- Protective against volume loss during delivery
- Protective for supine hypotension
- Response to systemic vascular resistance changes and increased capacitance

# Hematologic Changes In Pregnancy

## Red Blood Cells:

- Increased mass (patients will have increased MCV)
- Support for increased metabolic demand and oxygen consumption
- Vitamin and Nutrient deficiencies become more pronounced

# Hematologic Changes in Pregnancy

White Blood Cells (normal to have Leukocytosis of pregnancy)

- Abnormal when WBC  $> 20$ , increased blasts or immature WBC forms
- No change in the absolute lymphocyte count
- No change in the relative number of T and B lymphocytes

# Hematologic Changes in Pregnancy

## Platelets

- Counts decline in all pregnancies!!
- Asymptomatic women can have counts 80-150 K and is common
- Evaluate for pathology with acute distress, severe thrombocytopenia or symptoms

# Hematologic Changes in Pregnancy

## Coagulation/ Fibrinolysis

- Prothrombic state
- 20-200 % increase in procoagulants (Factors II, VII, VIII, X, XII, XIII); 2-4X's increase in vWF
- Reduced Anticoagulant Factors: Protein S deficiency
- Reduced Fibrinolysis: increased activity of fibrinolytic inhibitors

## Summary of hematologic changes associated with normal pregnancy

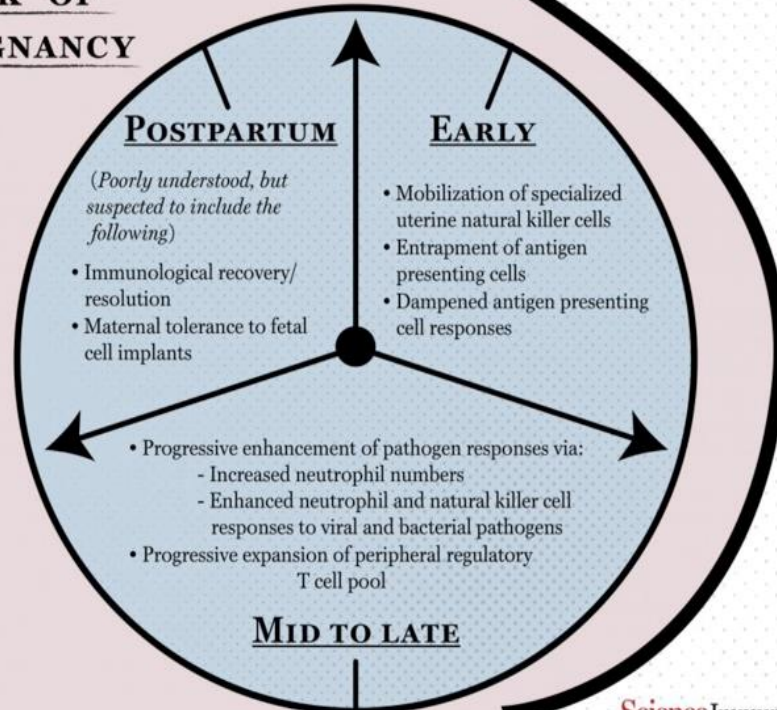
Plasma volume	Increased 30 to 50 percent
Red blood cell mass	Increased 20 to 30 percent
Hemoglobin concentration	Decreased
Red cell lifespan	Decreased slightly
Erythropoietin	Increased
Mean corpuscular volume	Increased slightly
Platelet count	No change to decreased slightly
White blood cell count	Increased (neutrophilia)
Lymphocyte count	No change
Monocyte count	No change
Basophil count	No change to decreased slightly
Eosinophil count	No change to increased slightly
Prothrombin time	Decreased slightly
Bleeding time	No change
Total protein S antigen, free protein S antigen, protein S activity	Decreased
Resistance to activated protein C	Increased
Fibrinogen, factors II, VII, VIII, X, XII, XIII	Increased 20 to 200 percent
Antithrombin, protein C, factor V, factor IX	No change to increased slightly
von Willebrand factor	Increased
Thrombin activatable fibrinolytic inhibitor, PAI-1, PAI-2	Increased
D-dimer	Increased

PAI: plasminogen activator inhibitor.

# Immunologic Changes in Pregnancy

- Allow for a semi-allograft fetus to persist and grow in pregnancy
- Cytotoxic adaptive immune responses are diminished, bypassed or evaded
- Regulative adaptive immunity is enhanced
  - JAK/STAT5 Signaling Pathway progressively increases
    - Differentiation of regulatory T cells
    - Maintenance of pregnancy
- Innate immunity remains intact
  - Maintains host defense against pathogens
  - Interaction with fetal tissues to promote successful implantation and maintenance of pregnancy

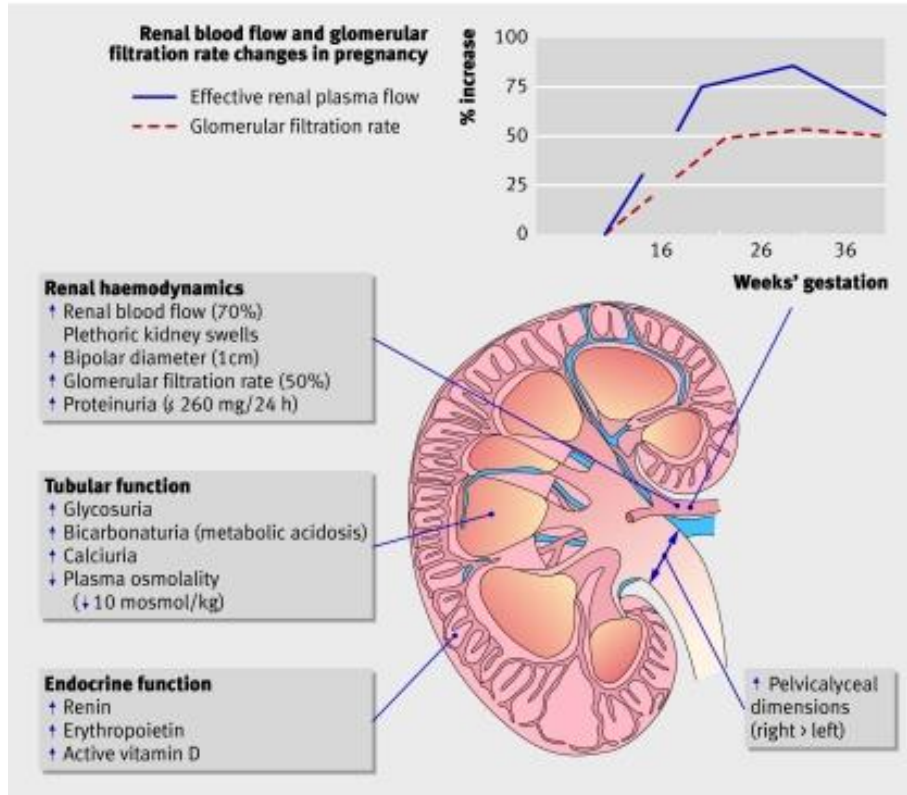
## AN IMMUNOLOGICAL “CLOCK” OF PREGNANCY



# Fetal Interactions

- Fetal trophoblast cells surround embryo and provide a protective barrier from the maternal immune system
  - Eventually becomes the placenta and has 3 distinct developmental pathways
  - Depending on differentiation have direct contact with maternal hematopoietic elements
  - Can differentiate to invade maternal decidua and spiral arteries

# The Kidney in Pregnancy



- 50% increase in GFR
- 70% increase in renal blood flow
- Kidneys enlarge on U/S

# Other changes

- Smooth muscle relaxation :
  - More reflux – secondary to smooth muscle relaxation
  - Constipation
- Anemia – dilutional
- Thought that NO is responsible for decrease in intravascular resistance (made by fetus?)

# Rheum disease and pregnancy

**TABLE 1** Interaction of pregnancy and some CTDs or vasculitis

Disease	Effect of pregnancy on disease	Risk of maternal complications in pregnancy	Risk for pregnancy complications	Risk for fetus/neonate
RA	Improvement in 48–75%	No	Moderate increase	Very rare
SLE	Flare in 50% of cases	Most frequent: haematological, and renal complications	Hypertension, pre-eclampsia, prematurity	Fetal loss, intrauterine growth restriction, low birthweight, neonatal lupus
APS	Aggravation	Thrombosis	Pre-eclampsia, prematurity, HELLP syndrome	Fetal loss, intrauterine growth restriction, low birthweight
SSc	No major effect on disease activity	Not more frequent than outside pregnancy	Prematurity	Reduced birthweight in premature infants
Takayasu arteritis	Unchanged in 72%, improvement in 20%	Progression of renal insufficiency, congestive heart failure	Hypertension in 30–44% Pre-eclampsia in 12–16%	Only at severe maternal disease, otherwise 85% good neonatal outcome
ANCA-positive vasculitis	Data insufficient to discern a particular effect	Renal and pulmonary disease	Pre-eclampsia, prematurity	Fetal loss, intrauterine growth restriction, low birthweight

HELLP: haemolysis, elevated liver enzymes low platelet.

# Rheumatoid Arthritis and Pregnancy

- Questionable data regarding subfertility issues
- >50% chance that symptoms will remit during pregnancy
- >90% will relapse postpartum
- Those with continued disease activity, flares or require steroid burst/maintenance have increased risk of preterm birth and lower birth weight

# Rheumatoid Arthritis and Pregnancy

- PARA: Dutch prospective pregnancy study 2002-2006
- Disease activity improved during pregnancy in 39% of patients with 38% experiencing a post partum flare
- Those with highest disease activity scores were those with moderate or high disease activity in the first trimester (De Man A &R 2008)
- Pregnancy may also decrease the risk of having an RA dx.
  - Women who have ever been pregnant have been reported to have a lower overall risk of RA. Hazes A&R 1990

# SLE and Pregnancy

- LUPUS=HIGH RISK PREGNANCY
- Multifactorial pathogenesis
- Heterogenous manifestations with potential to involve multiple organ systems
- Multiple autoantibodies to intracellular targets
- Pregnancy and postpartum period have increased risk of flares
  - Active disease prior to conception
  - Lupus nephritis
  - Quiescence x 6 months always recommended

# SLE Pregnancy management

- Start low dose aspirin (81-162 mg) in the first trimester (ACOG recommends this for all patients at high risk of preeclampsia)
- Monitor history, exam and lab test at least every trimester
- Continue hydroxychloroquine if already on it and consider adding if no contraindications for patient not taking the medication at conception

# Pregnancy Complications in SLE

- Maternal
  - Flares
  - Worsening of existing end organ disease
  - Overlapping presentation with pregnancy specific diseases
  - Thromboembolic disease
  - Infectious morbidities
  - Increased mortality

# Pregnancy Complications in SLE cont'd

- Fetal
  - Miscarriage/Stillbirth
  - Fetal growth restriction
  - Preterm birth with consequent neonatal morbidities/mortality
  - Congenital heart block
  - Neonatal Lupus

# Pregnancy Complications in SLE cont'd

- Obstetric
  - Abruptio
  - Cesarean section
  - Preeclampsia/Eclampsia
  - Increased postpartum hemorrhage

# Lupus Flare or Preeclampsia?



## **Difficult to determine with overlap of clinical findings**

Escalation of blood pressures

Proteinuria increases

Abnormal lab tests: BMP, CBC



## **Who to consider**

Women with lupus nephritis

Women transitioned from Mycophenolate Mofetil, ARBs and ACE-I

Steroid dependent

Can occur as a de novo insult of lupus nephritis

# Lupus Flare Versus Preeclampsia



## Consider Lupus if:

- Active urine sediment: RBC, WBC and casts
- Complement levels should go down
- Positive or increased ds DNA
- Leukopenia or normal WBC
- Uric acid levels are low
- Other organ system findings of disease-arthralgias, myalgias, skin manifestations



## Consider Preeclampsia if:

- Proteinuria only
- Complement levels are typically normal or even increased
- Leukocytosis
- Uric acid levels are elevated

# Antiphospholipid Antibody Syndrome Lab Criteria

- Lupus anticoagulant X 2 positive tests (12 weeks apart)
- Anti-cardiolipin Antibody IgG and/ or IgM  $> 40$  X 2 (12 weeks apart)
- Anti-Beta2-glycoprotein IgG and/ or IgM X 2 (12 weeks apart)

# Anti-phospholipid antibody syndrome clinical criteria

- Vascular Thrombosis
  - One or more clinical thrombosis of arterial, venous or small vessel thrombosis in any organ
- Obstetrical Complication
  - $\geq 1$  SAB  $> 10$  weeks
  - $\geq 3$  SAB  $< 10$  weeks
  - Preterm birth  $< 34$  weeks from preeclampsia/eclampsia, placental insufficiency

# Antiphospholipid Antibody Syndrome

- Prediction of adverse pregnancy outcome by the presence of lupus anticoagulant, but not anticardiolipin antibody, in patients with antiphospholipid antibodies. Lockshin MD, Kim M, Laskin CA, Guerra M, Branch DW, Merrill J, Petri M, Porter TF, Sammaritano L, Stephenson MD, Buyon J, Salmon JE *Arthritis Rheum.* 2012;64(7):2311.
  - Multicenter Prospective Observational Study 144 pregnancies in women with aPL to evaluate poor pregnancy outcomes
    - 39% with LAC had a poor pregnancy outcome versus 3% who did not have LAC
    - Women who had a prior thrombosis were more likely to have a pregnancy complication

# aPL Triple Positivity and Pregnancy Outcomes

- Antiphospholipid antibody profile based obstetric outcomes of primary antiphospholipid syndrome: the PREGNANTS study. Saccone G, Berghella V, Maruotti GM, Ghi T, Rizzo G, Simonazzi G, Rizzo N, Facchinetti F, Dall'Asta A, Visentin S, Sarno L, Xodo S, Bernabini D, Monari F, Roman A, Eke AC, Hoxha A, Ruffatti A, Schuit E, Martinelli P, PREGNANTS (PREGNancy in women with ANTiphospholipid Syndrome) working group. *Am J Obstet Gynecol.* 2017;216(5):525.e1. Epub 2017 Jan 30.
- Pregnancy failure in patients with obstetric antiphospholipid syndrome with conventional treatment: the influence of a triple positive antibody profile. Latino JO, Udry S, Aranda FM, Perés Wingeyer SDA, Fernández Romero DS, de Larrañaga GF *Lupus.* 2017;26(9):983. Epub 2017 Feb 7.
- Triple Antiphospholipid (aPL) Antibodies Positivity Is Associated With Pregnancy Complications in aPL Carriers: A Multicenter Study on 62 Pregnancies. Lazzaroni MG, Fredi M, Andreoli L, Chighizola CB, Del Ross T, Gerosa M, Kuzenko A, Raimondo MG, Lojaco A, Ramazzotto F, Zatti S, Trespidi L, Meroni PL, Pengo V, Ruffatti A, Tincani A *Front Immunol.* 2019;10:1948. Epub 2019 Aug 14.

# APS Pregnancy Complications

- Risk of thrombosis 5-12 %
- Fetal and recurrent pregnancy loss
- Preeclampsia: more likely to be severe and to occur preterm < 34 weeks
- Risk of fetal growth restriction 15-30%

# APL Management

- Decrease risk of thrombosis
- Modify potential risk of poor obstetric outcomes
- Low dose aspirin nightly 81- 162 mg
- Heparin or Lovenox in pregnancy and 6 weeks postpartum

# Management of APS during Pregnancy

- Baseline labs: CBC, CMP, 24-hour urine or protein/ creatinine ratio, SSA/ SSB antibodies
- Ultrasound surveillance of growth monthly in the 3<sup>rd</sup> trimester (earlier if previous pregnancy had growth restriction or poor pregnancy outcome)
- Fetal surveillance: NSTs and/ or BPP
- Delivery timing: 39 weeks unless other obstetrical indication exists
- Postpartum anticoagulation with at least 6 weeks of treatment

# Sjogrens Syndrome and Pregnancy

- Possibility of extraglandular involvement:
  - Interstitial lung disease and subnormal PFT
  - Primary Biliary Cholangitis
  - Celiac Disease
  - Interstitial Nephritis
  - Skin manifestations: Raynaud's and Xerosis
  - Arthritis and Myopathies

# Sjogrens Syndrome and Pregnancy Cont'd

- Chronic fatigue
- Thyroid Disease
- Increased risk of non- Hodgkin B cell lymphoma
- Secondary forms with overlapping RA, SLE or systemic sclerosis

# Management of Sjogrens Syndrome in Pregnancy

- Preconception evaluation
  - Medications in use to control disease and possible teratogenic profile, transition to pregnancy safe medication
  - Current organ system involvement and disease activity
  - Importance of dental care
- 1st Prenatal Visit
  - If not done, serologies for SSA/B and other relevant serologic testing, cryoglobulins, complement
  - CMP
  - Protein: Creatinine ratio
  - PFTs if not done
  - Dating of pregnancy
- Obstetrical Care
  - Routine surveillance of growth in third trimester
  - Antepartum testing for usual obstetrical indications, poor growth

# Anti Ro and risks during pregnancy

- Abs from maternal circulation cross the placenta and enter fetal circulation
- Does not matter if mom has a dx of autoimmune ds- only that she has SSA
  - Usually, high titer
- 1-4% risk of neonatal heart block 20% if mom had a prior child with heart block
- Occurs during about 18-24 weeks gestation
- When 3<sup>rd</sup> degree it is not reversible
- 7-16% risk of child with neonatal lupus (limited)
  - Skin
  - Liver
  - cytopenias
    - Bucato 2001 A&R Cimaz 2003 J Ped, Friendman Circ 2008

# Important to note

- Babies can progress to heart block after delivery as well
- Check EKG at birth if abnormal supervision by cardiology

# Pharmacologic Management of Rheumatic Disease in Pregnancy

- Disease modifying agent with best efficacy and least side effects
- Anticipation of pregnancy in reproductive age women
  - Contraception advice/counseling
  - Counseling regarding teratogenic potential of medications taken

# Medications to Avoid

- **Mycophenolate mofetil (CellCept)**
  - Should be stopped 6 weeks prior to conception, (ideally 12 weeks prior to conception per ACR)
  - Increased risk of miscarriage/stillbirth
  - Microtia/anotia, orofacial cleft, cardiac defects, facial dysmorphism



Figure 3. Lateral view of a 3-day-old newborn whose mother received a renal transplant and inadvertently ingested mycophenolate mofetil for the first 8 weeks of gestation. The infant had microtia and absence of the external auditory duct.

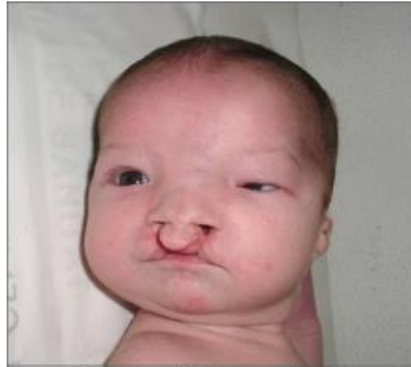


Figure 4. Frontal view of the same newborn, documenting ptosis of the left eyelid, upper cleft lip, hypertelorism, and micrognathia.

**Immunosuppressive Drugs and Pregnancy: Mycophenolate Mofetil Embryopathy.** Antonio Perez-Aytes, Ana Ledo, Virginia Boso, John C. Carey, Marta Castell, Maximo Vento. *NeoReviews*, Oct 2010, 11 (10) e578-e589

# Medications to Avoid

- **Methotrexate**
  - Folate antagonist
  - Abortifacient, CNS (ONTD related) abnormalities, skeletal abnormalities, facial dysmorphism, orofacial clefting
  - Widely distributed in tissues and can be detected in liver up to 4 months after last dose
  - Current guidelines are at least one menstrual cycle, but prefer 3 before conception
- **Leflunomide (Arava)**
  - Strong concerns for teratogenicity based on animal data
  - Not compatible with breastfeeding
  - Expert opinions suggest at least 3-6 months off medication before conception
    - Recommend blood testing to assure no levels are left in the body prior to conception
    - Can use cholestyramine and/or charcoal for rapid removal
- **Cyclophosphamide**
  - Alkylating agent and should be reserved for life threatening disease where no other medications can be used in pregnancy
  - Abortifacient, skeletal malformations, orofacial clefting, fetal growth restriction



# Medications to Avoid

- **Angiotensin Receptor Blockers and ACE Inhibitors**
  - Renal Tubular Dysplasia
  - Oligohydramnios
  - Skull ossification defects
- **Coumadin**
  - Vitamin K antagonist
  - Warfarin Embryopathy: neurologic abnormalities related to bleeding, microphthalmia, nasal hypoplasia, short limbs (bracydactyly), orofacial clefting, cardiac malformation
  - Dose related between 6-9 (up to 12) weeks



Figure 1. Depressed nasal bridge with a deep groove between the alae nasi and nasal tip.



Figure 2. Small nose on side profile view.

**[A Neonate with a Depressed Nasal Bridge.](#)** Anita Singh, Kirti M. Naranje, Banani Poddar. *NeoReviews*, Jun 2016, 17 (6) e352-e355

# Continue these Medications

## Hydroxychloroquine (Plaquenil)

- Long history of safe use in pregnancy for a variety of rheumatologic concerns
- Women who discontinue use near or during pregnancy demonstrated higher risks of preeclampsia and flares of rheumatologic disease
- Monitoring by Rheumatology for blood work and referral for eye exams
- May breastfeed

## Azathioprine/6-Mercaptopurine (Imuran)

- Continue in pregnancy
- Increased surveillance for fetal growth concerns
- Potential risk of preterm birth
- May breastfeed

## Tacrolimus (Prograf)

- Commonly used immunosuppressant in organ transplant
- Does not increase background risk of birth defects
- Monitoring of fetal growth in pregnancy
- Higher risk of hypertension related to its use

# Monitor Use of these Medications

- NSAIDS

- Unruptured follicle syndrome; temporary female infertility
- Not enough evidence, but some studies suggest an increased risk of gastroschisis and cardiac defects
- Known to increase the risk of PFO closure after 32 weeks
- Increased risk of oligohydramnios with third trimester use
- Delay in labor onset
- Safe for breastfeeding

- Corticosteroids

- Monitored use
- Conflicting data to suggest the *teeniest, tiniest* risk of orofacial clefting
- Steroid side effects-glucose intolerance, fluid retention, hypertension, bone demineralization, gastric ulceration, mood instability, insomnia, skin/tissue related issues, poor wound healing
- Safe for breastfeeding

# RA medications and pregnancy

**Table 1.** Summary of recommendations for safety of therapies for rheumatoid arthritis during pregnancy.

Therapy	FDA pregnancy category <sup>1</sup>	Toxicity concerns
<b>NSAIDs</b>	B	Concern for risk in third trimester exposure including closure of ductus arteriosus
<b>Corticosteroids</b>	B	Question of increased risk of cleft abnormalities
<b>Sulfasalazine</b>	B	No reported risk
<b>TNF<math>\alpha</math> inhibitors</b>	B	Question of concerns for VACTERL abnormalities
<b>Anakinra</b>	B	Inadequate data
<b>COX 2 inhibitors</b>	C	Concern for risk in third trimester exposure including closure of ductus arteriosus
<b>Hydroxychloroquine</b>	C	No reported risk
<b>Rituximab</b>	C	Reports of hematologic abnormalities, infection
<b>Abatacept</b>	C	Inadequate data
<b>Tocilizumab</b>	C	Inadequate data
<b>Tofacitinib</b>	C	Inadequate data
<b>Azathioprine</b>	D	Rare reports of congenital abnormalities but overall not felt to increase risk
<b>Methotrexate</b>	X	Aminopterin syndrome
<b>Leflunomide</b>	X	Toxicity in animal studies

<sup>1</sup>US Food and Drug Administration pregnancy category [see <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=201.57>]: A, controlled human studies show no risk; B, no evidence of risk in studies; C, risk cannot be ruled out; D, positive evidence of risk; X, contraindicated in pregnancy.  
NSAID, nonsteroidal anti-inflammatory drug; TNF, tumor necrosis factor; VACTERL, vertebral anomalies, anal atresia, cardiac defects, tracheo-esophageal, renal, and limb abnormalities.

# Biologic Medications and Pregnancy

- Most are monoclonal antibodies that target cytokines or cell surface molecules with a role in systemic or tissue specific inflammation
- Maternal to fetal transfer via the Fc portion in second and third trimester; previously we would discontinue these in 3<sup>rd</sup> trimester
- TNF blockers are commonly used in inflammatory bowel disease and arthritis
  - Data supports safe use in pregnancy in multiple studies
  - Do not contribute to birth defects, miscarriage, fetal growth restriction, preterm birth
  - Newborns exposed in utero had same risk of fungal, bacterial and viral infections as their unexposed children of disease matched women
  - No live vaccines (except rotavirus) are given before the first year of birth
- Certolizumab pegol lacks an Fc portion of the molecule shows little to no passage across the placenta
- Etanercept: big molecule unlikely to cross the placenta even in the third trimester

# Mother to Baby Website

- A branch of OTIS: organization of Teratology Information Specialists
- Collects info on moms exposed to drugs during pregnancy
- Has fact sheets on many of our medications on risk of exposure
- Runs studies
- Offers personal counseling to patients



# Breastfeeding

- LACTMED: NIH sponsored database on drugs and breastfeeding
- Download the app to have info handy



**LactMed**  
A TOXNET DATABASE

Drugs and Lactation Database (LactMed)

# Important Pearls to Remember

- Evaluate ALL reproductive age women for risk of pregnancy
  - Recommend appropriate pregnancy prevention/contraception
  - Those desiring pregnancy
    - Should have a preconception evaluation
    - Have achieved disease remission
    - Be transitioned off medications known to be teratogens and be stable on other DMARD safe for pregnancy x 6 months
- Lupus and Antiphospholipid Antibody Syndrome both have serious maternal, fetal and obstetric complications warranting close clinical surveillance by rheumatology and obstetrics

# Contraception

- Important to discuss family planning with patient due to teratogenic meds used to treat rheumatic disease
- About 50% of pregnancies in the U.S. are unplanned
- ACR strongly recommends use of emergency contraception with all patients including those with SLE and APS because risk is low compared to unplanned pregnancy

# Contraception for SLE patients

- Ideally use long acting reversible contraception such as: Copper IUD, Progestin IUD or Progestin implant (all <1 % failure rate in 1 year)
- Avoid estrogen-progestin patch because this results in > estrogen exposure compared with oral or vaginal products
- Avoid estrogen containing products in moderate-severe disease activity or lupus nephritis patients

# Contraception for APS patients

- Avoid combined estrogen- progestin products as estrogen can increase the risk of thromboembolism
- Progestin- only methods are thought to be lower risk for this population
- Progestin only pills are another option if the patient does not want IUD

# Thank You

- Dr Joann Zell University of CO rheumatology clinic
- Dr Julie Scott University of CO Maternal Fetal Medicine

Questions?

