



# Rheumatoid Arthritis: Considerations for Pregnancy

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# Outline

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- Natural history of RA in pregnancy and postpartum
- DMARD and Biologic use during pregnancy
- Breastfeeding Issues
- Males and Medications

# Rheumatoid Arthritis in Pregnancy

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- 70-80% remission rate during pregnancy
  - Starts in first trimester
  - Age, disease duration, disease severity, RF do not predict pregnancy outcome
- 90% flare in postpartum period, within the first 3 months
- No increased risks of fetal morbidity/loss
  - 1 study showed lower birth weight
- No increase in maternal morbidity

# Immunology of Pregnancy

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Occur at maternal-fetal interface to prevent “rejection” of the fetus

- Change in cytokine profile Th1→Th2
- ↓ Activity of NK cells
- ↑ Soluble TNF- $\alpha$  receptors
- ↑ Plasma levels of IL-1 antagonist
- ↑ Complement component synthesis
- Altered neutrophil function
- Development of anti-HLA class II antibodies

# HLA disparity and RA

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- 41 RA patients, 57 pregnancies
- Serologic and DNA techniques to study HLA antigens
- More maternal –fetal disparity in HLA-DR and DQ antigens in pregnancies with remission or improvement in RA
- Maternal response to paternal HLA antigens may have a role in pregnancy-induced RA remission

# Hormones and Pregnancy

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- ↑ DHEA, cortisol, estrogen, progesterone, and norepinephrine in pregnancy
- Contribute towards alteration to Th2 immune response
- Patients with increased levels of pregnancy related protein alpha-2 (PAG) were more to go into remission / improve

# Flare-Ups Post Partum

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## ○ Possible Causes:

- ↓ Anti-inflammatory steroid levels
- ↑ Levels of prolactin (pro-inflammatory)
- Change in neuroendocrine axis
- Change from Th2 to Th1
- Breastfeeding:
  - Controversial
  - Some studies suggest assoc with flare
  - ? Related to prolactin

# Medication Use in Pregnancy

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Preconception counseling about teratogenicity and adverse effects must be done prior to conception

# Medication Use and Pregnancy

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- Data is NOT from clinical trials
- Unethical to include pregnant women – thus, data is from case-controlled/cohort studies/case series and reports
- Animal pregnancies differ from human
- Limited safety information
- Many confounders

# FDA Pregnancy Categories

Category	Description
A	Adequate and well-controlled studies have failed to demonstrate a risk to the fetus
B	Animal studies failed to demonstrate a risk to the fetus - no adequate studies in humans
C	Animal studies have shown an adverse effect on the fetus – no adequate human studies but potential benefits may warrant drug use
D	Positive evidence of fetal risk from investigational or marketing studies in humans, but potential benefits may warrant drug use
X	Positive evidence of human fetal risk – risk involved outweighs potential benefits

# NSAIDs

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- Cross the placenta
- First trimester:
  - Can interfere with implantation
  - Ibuprofen – ? ↑ gastroschisis (1 study)
  - Naprosyn – ? ↑ in oral clefts (1 study)
  - ? ↑ in cardiac defects (2 studies)
  - ? ↑ risk of spont abortion (1 study)
- Consensus: No conclusive data – intermittent use probably OK in early pregnancy

# NSAIDs in Third Trimester

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- Maternal Effects:
  - Prolonged gestation and labor
  - Increased peripartum blood loss and anemia
- Potential Fetal Effects:
  - Premature closure of ductus arteriosus → pHTN
  - Impaired renal function → oligohydramnios
  - Increased cutaneous and intracranial bleeding
  - Necrotizing enterocolitis and ileal perforation
- Consensus:
  - Stop 6-8 weeks before delivery
  - Prefer short acting NSAIDs (ibuprofen, diclofenac)

# Corticosteroids and Placenta

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- Hydrocortisone, cortisone:
  - 10% of maternal dose crosses placenta
  - Thus, if needed for mother, use prednisone, hydrocortisone, cortisone
- Dexamethasone, Betamethasone:
  - 100% of maternal dose crosses placenta
  - Thus, used to treat fetus

# Corticosteroids

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- Low dose (<20mg) considered safe
- High doses:
  - Maternal HTN
  - Gestational DM
  - Osteoporosis
  - PROM
- Around time of conception:
  - 3-6 fold ↑ risk of cleft lip +/- palate

# Corticosteroid Recommendations

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- Generally safe
- Use lowest possible dose
- Oral calcium / vitamin D should be given
- May need “stress dose” around labor and delivery
- Neonate should be monitored for adrenal insufficiency and infection

# FDA and Anti-Inflammatories

Class	Agent	FDA	Comments
NSAIDs	Celecoxib	C	Minimal first and second trimester risk
	Diclofenac	C	
	Ketorolac	C	
	Prixicam	C	Significant maternal and fetal effects in third trimester
	All Others	B	
	3 <sup>rd</sup> Trimester	D	
Corticosteroids	Prednisone	C	Minimal risk
	Cortisone	D	
	All others	C	



# DMARDs in Pregnancy

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# Methotrexate

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- Known teratogenic
- Abortigenic in high doses
- Fetal defects include:
  - Craniofacial abnormalities
  - Limb defects
  - CNS defects – anencephaly, hydrocephaly, meningomyelopathy

# Methotrexate in Pregnancy

Outcomes	Chakravarty 2002	Donnenfeld 1994	Kozlowski 1990	Lewden 2004	Ostensen 2000	Ostensen 2007
MTX Dose	Low	7.5-42mg	7.5- 10mg	10.5mg	5-15mg	Low
# Exposed	31	14	8	23	4	1
Miscarriages	7 (23%)	4 (29%)	3 (38%)	4 (17%)	1 (25%)	1 (100%)
Live births	23 (74%)	10 (71%)	5 (62%)	19 (83%)	3 (75%)	0
Birth defects	3 (9%)	1 (7%)	0	1 (4%)	0	0

# Methotrexate: Management

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- MTX should be stopped 3 cycles prior to conception
- Folic Acid should be continued
- Critical period of exposure is between 6-9 weeks post-conception
  
- Controversial – should pregnancies on MTX be terminated??
  - Suggestion: If dose < 15mg then continue pregnancy. For higher doses, ? Recommend termination

# Leflunomide

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- Extremely teratogenic – congenital malformations in animal studies
- Absolutely contraindicated in pregnancy
- Active metabolite detectable in plasma for up to two years

# Leflunomide in Pregnancy Reports

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- De Santis et al., 2005
  - 3 patients with RA and LEF
  - 2 terminated, 1 with healthy live birth
- Chakravarty et al., 2003
  - 10 patients with LEF during pregnancy
  - No fetal malformations reported

# Leflunomide: Management

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- Drug needs to be eliminated prior to conception (can take 2-3 yrs)
- Can use Cholestyramine 8g tid x 11d to eliminate prior to conception
- Need serum levels  $< 0.02\text{mg/L}$  x 2, 2 weeks apart prior to conception
- After cholestyramine, wait three cycles

# Sulfasalazine

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- Considered generally safe in pregnancy
- 3 large studies in IBD patients (N >300)
  - No maternal or fetal toxicity found
- 2 case-controlled studies
  - 2-3 fold risk of neural tube defects, cardiovascular defects, oral clefts
  - ? Related to folic acid antagonist action
  - Diminished with folic acid supplement

# Sulfasalazine: Management

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- Considered safe
- Low risk
- Should be given with folic acid supplementation

# Hydroxychloroquine

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- Crosses placenta in humans
- No fetal toxicity in our doses (6.5mg/kg)
- Multiple case control trials (n=36, 133, 35) showing no fetal abnormalities
- Potential risk of fetal retinal toxicity at higher doses

## Management:

- Considered safe
- If RA in remission, stop during pregnancy, but cannot avoid fetal exposure

# Azathioprine

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- Most studies come from transplant pts
- Crosses placenta but fetal liver lacks enzyme to convert to active metabolite
- Thus, fetus is protected from teratogenic effects

# Azathioprine in Pregnancy

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- Reports of 190 babies with IBD or SLE
  - No increased risk of structural defects
  - Noted complications:
    - IUGR, cytopenias
    - Small for gestational age
    - PROM
  - But ? Related to underlying disease
- Management: Must do risk/benefit analysis - ?safe if severe underlying dz

# FDA and DMARDs

Agent	FDA	Comments
Methotrexate	X	Contraindicated
Leflunomide	X	Minimal human data; contraindicated
Sulfasalazine	B	Low risk
Hydroxychloroquine	C	Potential retinal toxicity; no cases reported
Azathioprine	D	? Risk of IUGR, PROM, SGA but may be related to underlying dx



# Biologics in Pregnancy

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# Biologics in Pregnancy

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- Animal studies with no evidence of maternal or embryo toxicity
- Classified as Pregnancy Class B by FDA
- More data with post-marketing surveillance
- Most case reports with exposure in first trimester only
  
- Orozco et al, 2005
  - 84 patients on TNF antagonists
  - Outcomes same as general population

# Etanercept

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- Chakravarty et al., 2003
  - 14 RA pts with Enbrel in pregnancy
  - No malformations / complications
- Multiple case reports with Enbrel and RA
  - No abnormalities reported
- OTIS Group
  - 32 patients with Enbrel
  - No abnormalities found
  - ? Higher rate of prematurity

# Infliximab

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- No adverse maternal/fetal abN reported
- Katz et al, 2004
  - 58 Crohns with 1<sup>st</sup> trimester exposure
  - No risk of pregnancy loss
  - 3 with structural problems
- Remicade Safety Database (Centocor)
  - 133 pregnancies with data on 65 pts
  - No adverse outcomes

# Adalimumab

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- Very limited data
- OTIS Group, 2006
  - 29 first trimester exposures
  - No difference with general population
  - Normal birth weights
- 4 case reports throughout pregnancy with Crohns – healthy, live-born children

# Rituximab

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- Rituximab crosses placenta from week 16 onwards – fetal levels similar to maternal
- 3 Published reports (2 NHL, 1 AIHA)
  - 2 exposed in 1<sup>st</sup> trimester only – found lymphopenia, normal B cells in fetuses
  - 1 exposed throughout – B cell depletion in fetus
  - Spontaneous recovery of B cells
  - All had normal response to vaccines

# Rituximab Cont'd

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- Unpublished safety update, 2005
  - 24 pregnancies
  - 10 with known outcome
  - 1-8 months prior to conception
  - Malignancy patients
  - Normal live infants in all, no congenital abnormalities
  - 2 low WBC – recovered
  - 1 anemia and lymphopenia - recovered

# Abatacept

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- Known to cross the placenta
- High dose treatment in pregnant rats – no malformations or adverse outcomes
- No human pregnancy experience
- Company recommends waiting 10 weeks after last dose until conception

# Biologics: Management

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- Minimize exposure during pregnancy
- Stop TNF inhibitor as soon as patient is pregnant
- ? Benefit of using short acting drug in women who are planning pregnancy

# Biologics and FDA

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Agent	FDA	Comments
Etanercept	B	No documented animal risk; Human risk undetermined
Infliximab	B	
Adalimumab	B	
Abatacept	C	
Rituximab	C	



# Breastfeeding

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# Drugs That Are Thought to be Safe

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- NSAIDs & Acetaminophen
- Corticosteroids
  - Peak milk levels - 2 h after ingestion
  - Child receives < 0.1% of maternal dose
- Antimalarial agents
  - Peak milk levels at 2h; decline 9h
  - Child receives 2% of maternal dose
  - Case reports – no retinal, motor, growth abN
- Sulfasalazine
  - Undetectable levels in breast milk but high levels of metabolites found
  - Case report of bloody diarrhea in infants
  - Thus, use caution and monitor infants

# Drugs with Potential Risks

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- Azathioprine
  - 0.1% of maternal dose in breastmilk
  - 17 case reports – infants with normal growth, development, blood counts
- Methotrexate
  - After oral dose 22.5mg – milk level 2.3 mg/l
  - One case report – limited data
- Leflunomide – no data
- TNF Inhibitors
  - Small amounts of Etanercept & Infliximab detected in breast milk
  - Clinical significance unknown



What about men?

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# Men and Medication

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- Limited data
- Must consider teratogenicity and fertility issues

# Drugs to consider

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## Decrease Sperm:

- Methotrexate
- Leflunomide
- Sulfasalazine
- ? Azathioprine
  
- Cyclophosphamide – irreversible germ cell dysfunction

## ? Teratogenic

- Methotrexate – stop 3 months before conception
  
- Leflunomide – eliminate with cholestyramine before conception

# Summary

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- Most RA goes into remission during pregnancy and flares post-partum
- Counseling on medications is important prior to conception
- Pregnancy safety data is of poor quality....  
Must weigh risks and benefits
- Breastfeeding – decisions individual!



Questions??

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