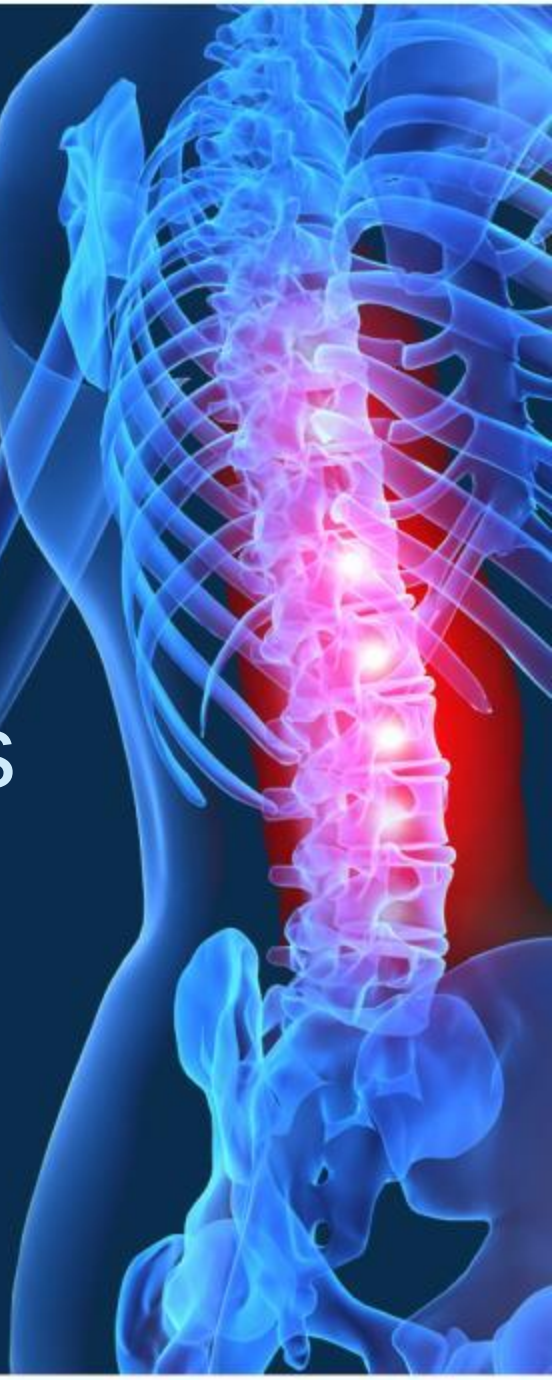
Annual Rheumatology & Therapeutics Review for Organizations & Societies



Pregnancy and Rheumatoid Arthritis

RA Pregnancy – Myths & Facts

- Rheumatoid arthritis does not affect fertility
- Pregnancy induces remission in 80% of RA pts
- Be off MTX x 3mos before trying to conceive
- Biologics are contraindicated in pregnancy
- Paternal drug exposure doesn’t affect the fetus
- Avoid drugs w/ breastfeeding (found in breastmilk)
- Fetal malformations increased w/ MTX, leflunomide

Did You Know?

- Before 1993, women were not included in RCTs
- >50% of Pregnant RA pts TNFi before
- 30% of RA Preg patients continue TNFi during preg
- > 50% of IBD patients continue TNFi during preg
- OTIS-Organiz. of Teratology Information Specialists published 2 papers (71 pts) on DMARDs/Pregnancy
  - Autoimmune registry - studied multiple biologics (>1900 pts), worldwide collab, counsels >100,000 callers/yr
- FDA has changed “guidance” on pregnancy and PI

Dictionary

- Parity: #of times a female has given birth
- Gravidity = Pregnancy
- Fertility: # children born to a woman
    - Lack of = Infertility
- Fecundity: probability of conception/reproduction
    - Lack of = Sterility
- Spont. Abortion (miscarriage): fetal death < 20 wks
- Still Birth: fetal death > 20 weeks
- Premature birth: < 37 weeks gestation
- Low birth weight: < 2500 grams

Pregnancy is a lot like Cancer….

- Rheumatologists are generally uninvolved in the care of their pregnant patients.
  - Pregnancy becomes more impt than arthritis
  - Pregnancy is managed by OB/GYNs (oncology)
  - Infrequent event
  - Belief that most will improve without my input
  - Fear of drug exposure (Pt, MD)
  - Lack of consensus on medical management of the patient

Pregnancy is not an adverse event.

However a flare of disease activity is, and compromises both maternal health and possibly infant outcomes.

32 yo F with RA x 9 yrs, prev Rx w/ HCQ, MTX, ETN, now on Adalimumab + Pred. She's about to be married – wants to know if she can have babies?
What do you tell your patient

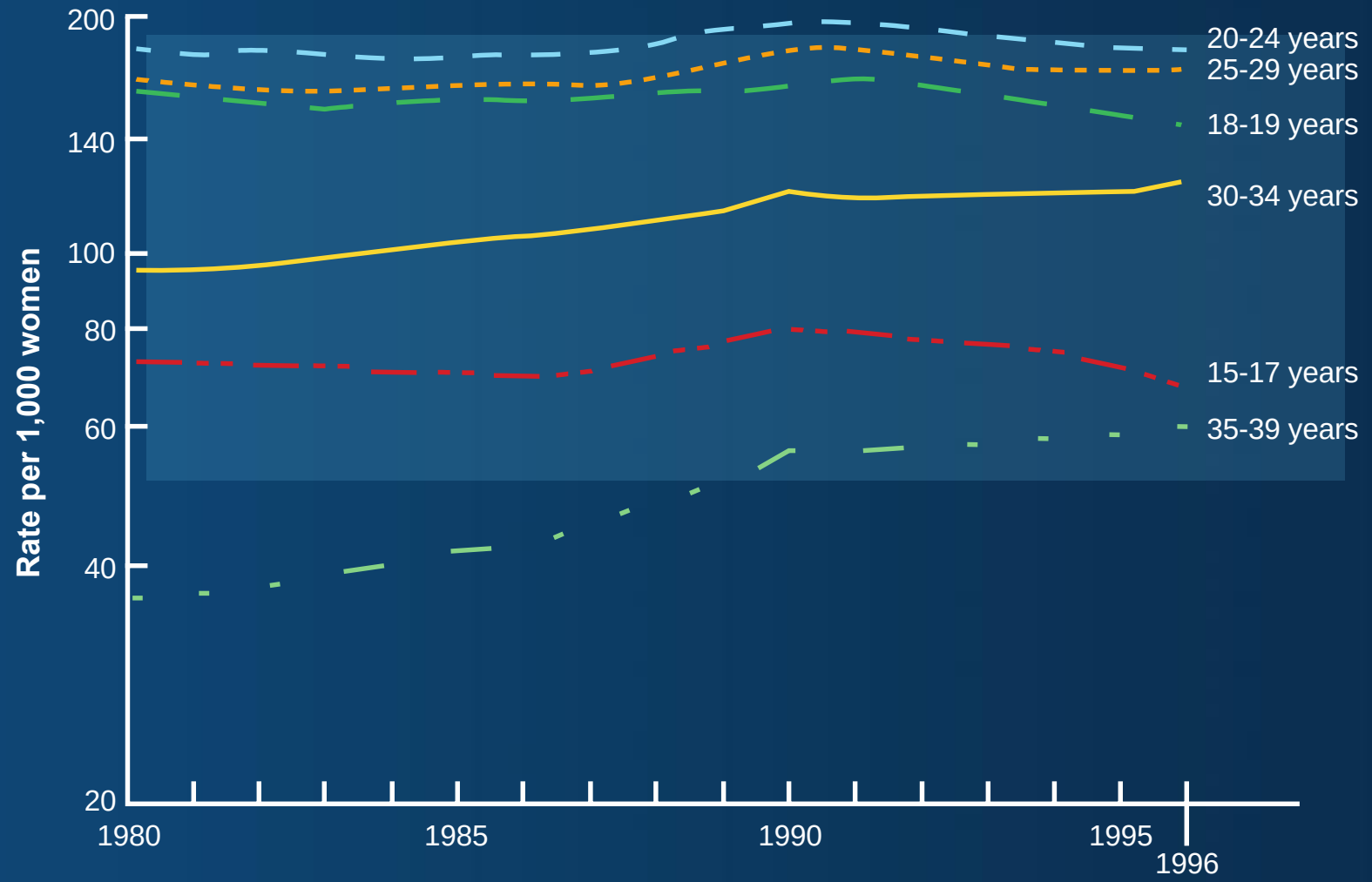
1. Needs to get her pre-pregnancy advice from OB
2. Methotrexate may impair her future fertility
3. RA patients have normal fecundity/fertility
4. Her fertility is related to past RA activity
5. Her fertility is related to current RA activity

RA & Pregnancy: Background

- Fertility rates in RA not different than controls.
- Average RA female has ~3 lifetime pregnancies (with >2/3 conceived prior to diagnosis of RA)
- POST- Dx: RA pts have:
  - fewer births (1/3 to 1/6 expected)
  - a shorter time span of reproduction
  - longer inter-pregnancy intervals
  - reduced subsequent pregnancy rate

Bogas M, Leandro M. Biologic therapy and pregnancy. A systematic literature review. Acta Rheumatol Port. 2011 Jul-Sept;36(3):219-232.
Mitchell K, et al. The management of rheumatic diseases in pregnancy. Scand J Rheumatol 2010;39:99–108.

Pregnancy Rates by Age Bracket
Average Estimate 100/1000 = 10%



NOTE: Rates are plotted on a log scale

CDC Jan 2000

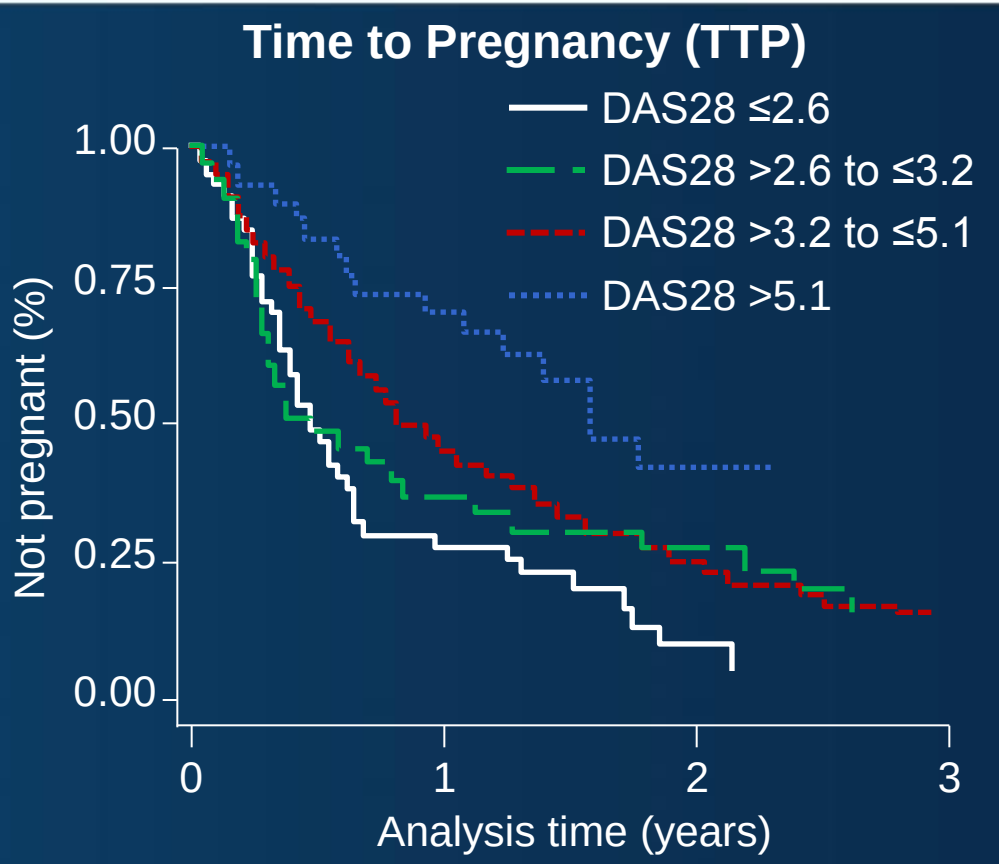
Parity, Fertility in RA

Lower fertility rates in RA – 0.88, 0.91 More treated for infertility (9.8 % v 7.6%)	RA pts who conceive slightly older (30yrs)
RA were 31% more likely to be childless at diagnosis	RA does not correlate with multiparity or nulliparity

Golding A, Rheum Dis Clin NA 2007; 33:319–343 Walenius M. Scand J Rheumatol. 2012;41:202-7
Jawaheer. Arthritis Rheum. 2011 Jun;63(6):1517-21

Reduced fertility in women with RA: Influence of disease activity and medication use

- RA: fertility impaired and time to pregnancy (TTP) may be prolonged
- PARA study – prospective cohort of RA pregnant women (2002–2010)
- 245 patients: 58% fertile; 42% subfertile (TTP >12 months)
- Prolonged TTP associated with:
  - Older age
  - Nulliparity
  - ↑ DAS28
  - Prednisone >7.5 mg/day
  - NSAID use



Longer TTP in RA associated with older age, nulliparity, higher disease activity, NSAID use or u prednisone use with daily dose >7.5 mg

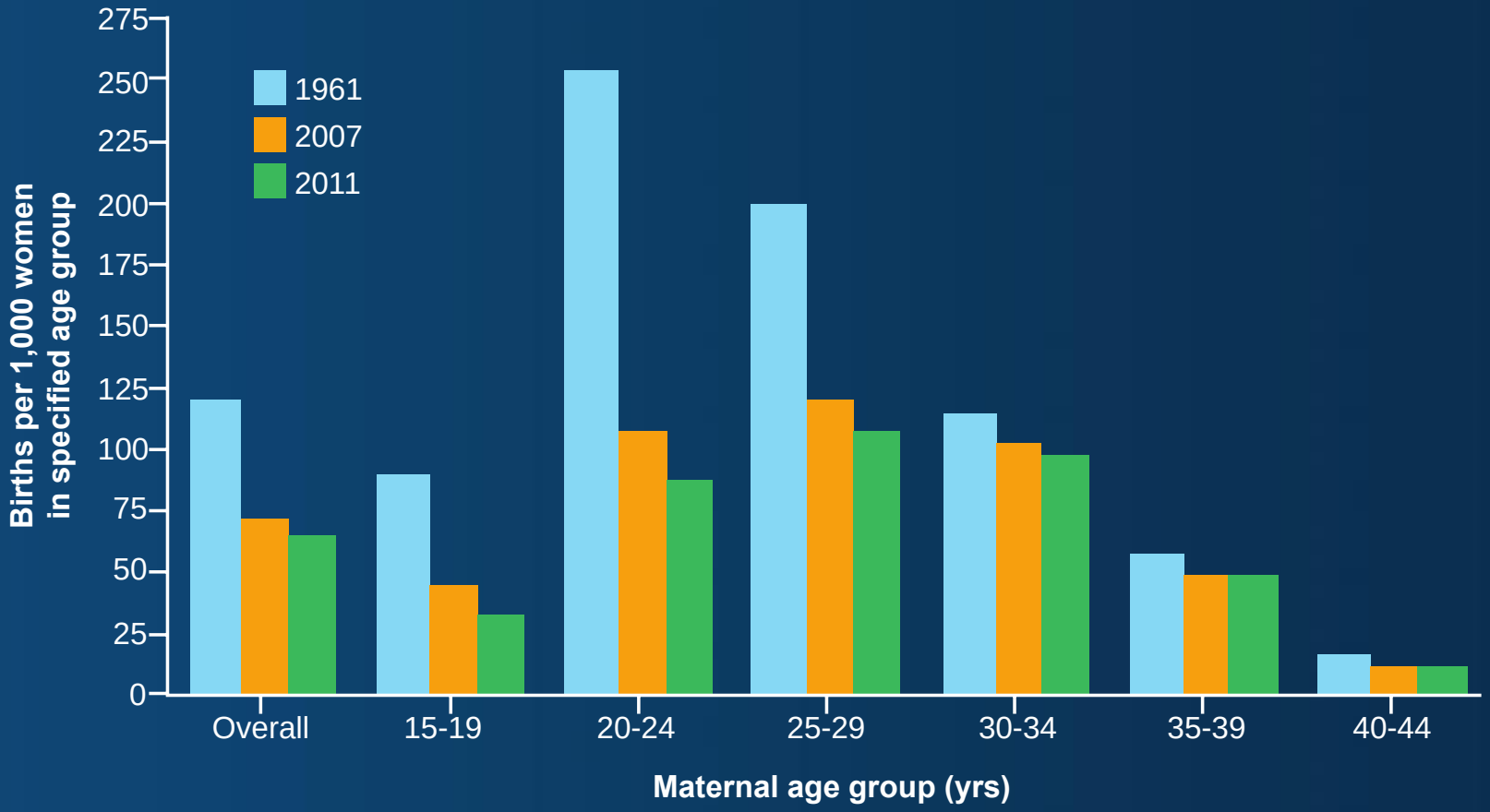
Brouwer J, et al. ACR 2013, San Diego, #2681

Frequency of Pregnancy in RA

- Not formally studied
- Using inferred population statistics
  - **800-2100** RA annual births to RA patients in US
- **1,425** RA pregnancies in 2002
    - (Nationwide Inpatient Sample of Healthcare Cost and Utilization Project)

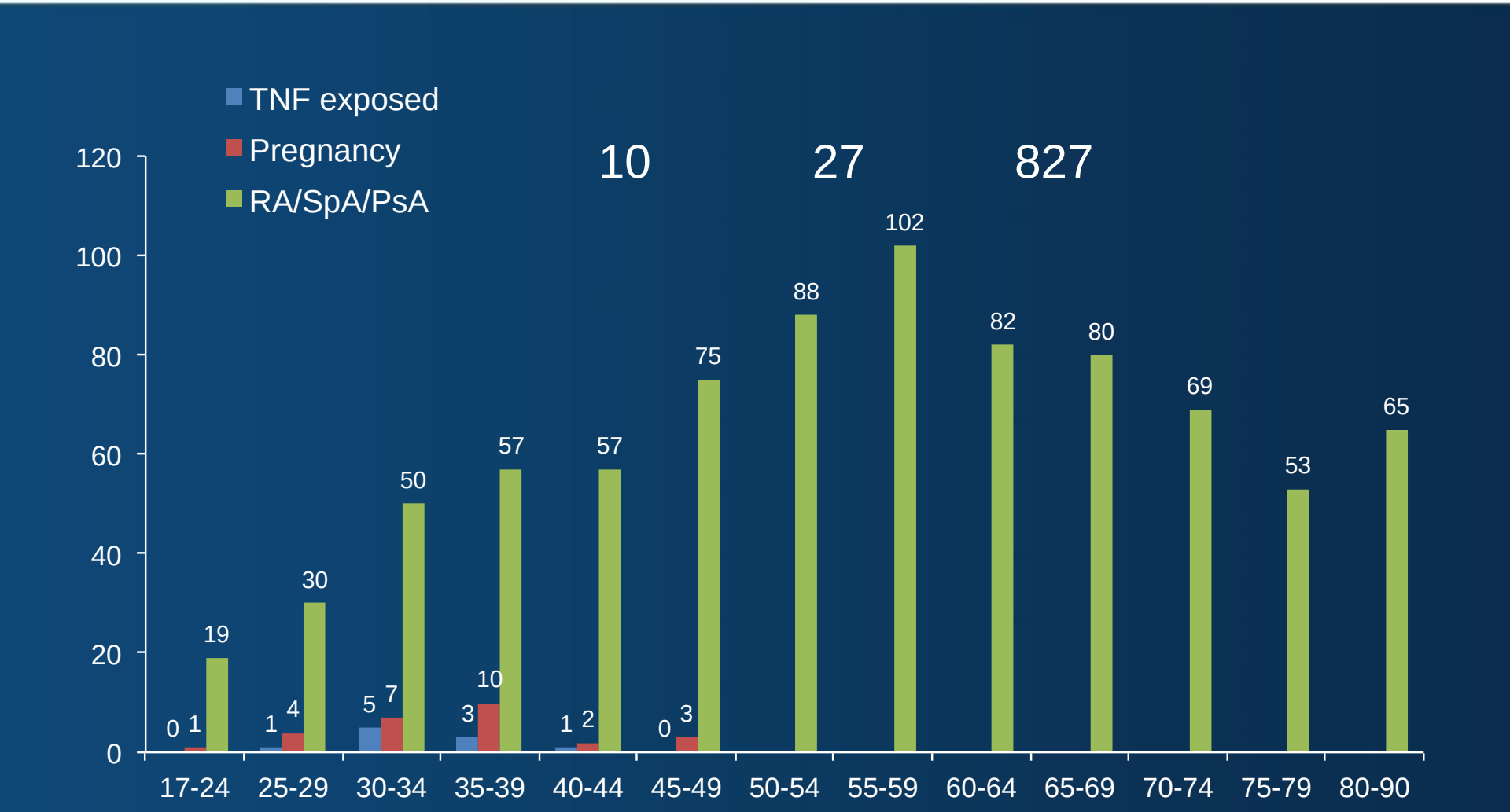
Golding A, Rheum Dis Clin NA 2007; 33:319–343 Chakavarty EF. Arthritis Rheum, 54 (3) (2006), pp. 899–907

US Birth Rates* Women 15-44 Yrs 1961, 2007, 2011



MMWR November 30, 2012 / 61(47);978

Arthritis Care & Research Patients



What Percentage of RA Women Who Become Pregnant Will Go Into Remission Off Drugs?

1. 80%
2. 60%
3. 50%
4. 35%
5. 15%

Rheumatoid Arthritis Improves During Pregnancy

- Hench in 1938: 90% of women had relief of arthritis during pregnancy.
- Subsequently 70-80% remissions during preg
  - Starts in first trimester
  - Age, disease duration, disease severity & RF do not predict pregnancy outcome

(Subjective, retrospective, small #s, no metrics)

- Recent cohort studies refute these #s

RA Outcomes During Pregnancy*

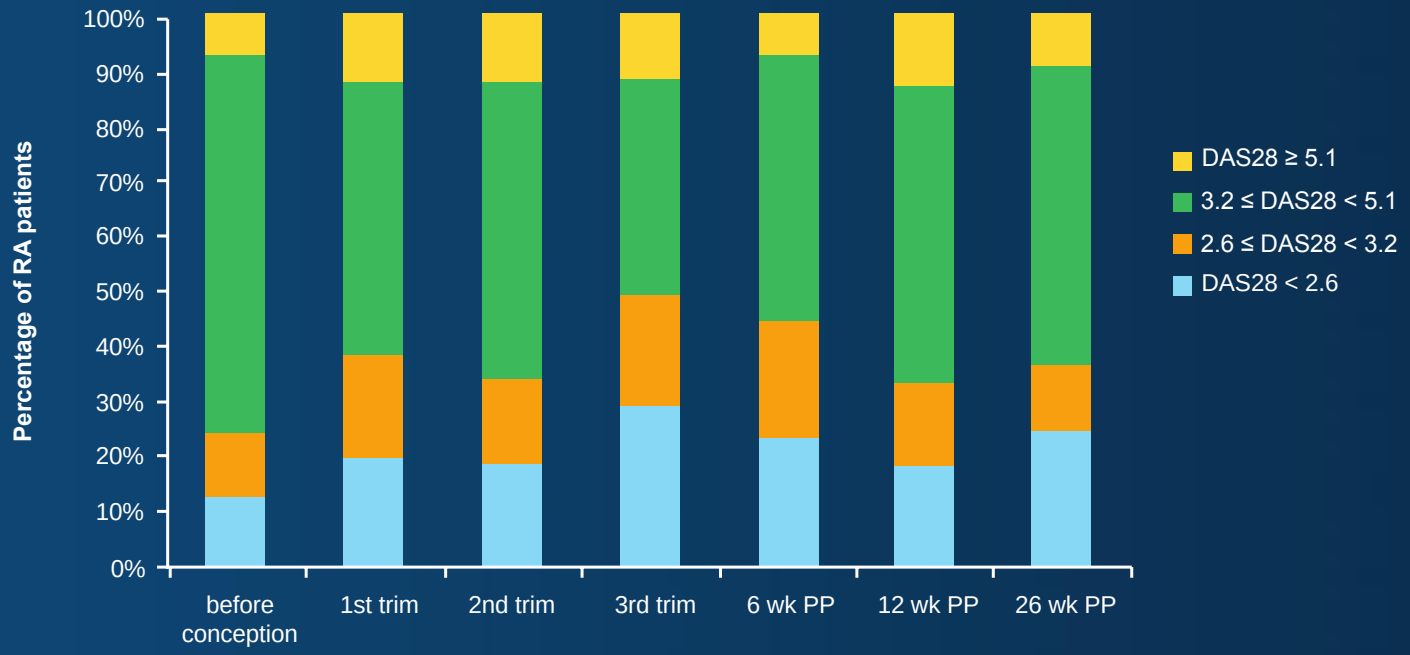
Reference	Study type	# patients (pregnant)	Improved during Preg %	Post-partum exacerbation %
Hargreaves	Retrospective	10 (11)	91	91
Hench 1938	Retrospective	20 (34)	90	90
Klipple Cecere	Retrospective	93 (114)	77	82
Oka 1953	Retrospective	93 (114)	77	81
Neely1977	Retrospective	56	63	
Ostensen1984	Prospective	31 (49)	75	62
de Man	Prospective	118 (118)	47 (75 RF-)	33–42
Ostensen	Prospective	10	70	60
Barrett 1999	Prospective	140	66	75
Nelson	18 prosp;39retrospc	41 (57)	60	–
de Man	Prospective	84	39	38

* Caution: these are small retrospective analyses, using various definitions of disease activity and improvement; often with pt recall

Adapted from Hazes, Rheumatology . 2011 November; 50(11): 1955–1968.

RA Activity with Pregnancy

- 84 RA pts: ½ moderate dz in 1st trimester & ½ have mod-high dz activity by 3rd trimester
  - Only 27% DAS remission by 3rd trimester
  - Doubling of LDAS from pre- to 3rd trimester



De Man Y. Arthritis Rheum. 2008 Sep 15;59(9):1241-8.

3rd Trimester Disease Activity

	Remission (*3rd Trimester)	Moderate/High Disease activity
De Mann 2008	27%*	52%*
Barrett* 1990	16%*	-
Nelson*	39%*	-
Langen 2013	-	60% flare during
Cush 2012	36.5%	27%

Remission defined as using no antirheumatic drugs and No painful or swollen joints

Pregnancy and Fetal Concerns

Disease	Maternal Complications	Fetal Complications
SLE	Reduced fertility (CTX Rx)	Rash neonatal lupus
	Flare during and postpartum	Congenital complete heart block
	Hypertension, Pre-eclampsia	IUGR, Premature birth, Fetal loss
APS	Thrombosis, Pre-eclampsia HELLP, Thrombocytopenia	IUGR, Fetal Loss, Prematurity, Neonatal thrombocytopenia
RA	Postpartum flare; RA onset during & post pregnancy	Preterm delivery and low birthweight

Rheumatoid Arthritis in Pregnancy
Post-Partum Events

- 90% flare in postpartum; within 3 months
- Oka: RA recurrence by month post-partum:

  Mo 1: 36%

  Mo 2: 69%

  Mo 3: 85%

  Mo 4: 98%

- No increased risks of fetal morbidity/loss
  - 1 study showed lower birth weight
- No increase in maternal morbidity

Oka M. Ann Rheum Dis, 12 (1953), p. 227

27 yo F with RA x 3 yrs is unable to get pregnant. She is on HCQ, doing well w/ CDAI 3, DAS 1.8. She is unable to get pregnant x 18mos and heard that TNFi can be used to get pregnant.
What do you do?

1. Advise she consult w/ infertility specialist
2. Start her on certolizumab 200 mg EOW
3. Stop HCQ and start prednisone 5 mg qd
4. Encourage her to adopt a rescue pit bull

TNF Inhibitors and Infertility

- Numerous case reports of subfertility alleviated by TNF inhibitor Rx
- Winger et al, treated 100 women w/ recurrent failure of IVF
  - ADA + IVIG + heparin w/ 100% pregnancy and 88% take-home baby success
  - No increase in deformity rates
- No controlled RCTs

Sills Am J Reprod Immunol. 2001 Nov;46(5):366-8. Resvani A. Indian J Pharmacol. 2008 Nov;40(6):276-7.
Clark DA. Am J Reprod Immunol. 2009 Feb;61(2):107-12. Winger EE. Am Jt Reprod Immunol. 2011 Sep;66(3):237-41

TNF-Inhibitors and Infertility

- 50→70% of all conceptions fail;
- recurrent loss 1-3% couples
- Maternal Tolerance; ? Th2 biased response
  - ? role of complement inhibitory proteins, maternal regulatory T cells, immunoregulatory cytokines in placental milieu
- ? Role of innate immune system in pregnancy loss
  - TNF inhibition improves pregnancy outcomes in antiphospholipid antibody treated mice
- In animal models, immune driven systemic inflammation → ovarian failure/insufficiency → pregnancy loss

Berman J, J Immunol 2004;174:485-90
Erlebacher A, et al. J Clin Invest 2004;114:39-48
Salmon JE, J Clin Invest 2004;114:15-17
Wallace D, Weissman M. J Rheumatol 2003

Pregnancy and Risk of RA Onset

- During Pregnancy: Low/Reduced risk of RA onset (0.3)
- Post Partum: 5x increased risk of RA onset 1st 3mos postpartum
- Parity and RA onset Risk?
  - Inconsistent; some say ↑risk in nulliparous

Pregnancy: Effect of RA and Biologics

- 1712 Pregnancies
- 636 women in BRASS;
  - 86% 1st time prior to RA onset
  - 14% after RA onset

BRASS Registry

	National Studies	Pregnancy pre-RA onset	Pregnancy Post-RA onset
Miscarriages	10 -15%	15.8%	20.1%
Birth weight <2.5 Kg	8.3%	5.8%	8.9%

Johnson D I et al ACR 2008 abstr#1387; 1388;
Friden C et al ACR 2008 Abst#729;
Snoeckx Y et al abstr#702

Adverse Outcomes in RA

- RA & Pregnancy, more likely to have:
  - Low birth weight
  - Small for gestational age
  - Preeclampsia
  - Cesearean sections
  - Adverse preg outcomes (Sp Ab, Stillbirth)
    - More adverse outcomes associated w/ higher HAQ, DAS28

Lin H Ann Rheum Dis. 2010 Apr;69(4):715-7 Camacho ACR 2011

RA and Pregnancy, Worse Outcomes
The Norfolk Arthritis Register (NOAR)

- Female reproductive factors (parity, menopause status, adverse pregnancy outcomes -APOs) may impact upon a woman's likelihood of developing RA
- APO: spont abortion or stillbirth.
  (NOAR APO rate = gen pop)
- 397 (25%) RA pts had ≥1 APO before symptom onset
  - 125 (8%) women had 2+ APOs and 47 (3%) had 3+ APOs.
- Median onset age was significantly younger for women w/ Hx of APOs vs no APOs (52 vs. 55 yrs)
- Women w/ Hx of 2+ APOs had significantly higher HAQ and DAS28 scores over time than women with no APOs
  - More pronounced, in women with 3+ APOs

Camacho ACR 2011

Contraceptive Use

- RA: meta-analysis of 6 different studies w/ progesterone (5) and 1 estrogen showed no pattern of improvement or worsening*
  - Some reports suggest Protective effect
  - Same for IBD meta-analyses
- SLE: meta-analysis of 13 studies
  - Combination OCP does not lead to increased flares or worsening activity in inactive or stable active SLE.
  - Progestogen OCP: No increase in disease activity
  - Possible increased thrombosis in +APL Abs & Hx of OCP use
  - Copper intrauterine device is not associated with worsening disease activity or infection in women with SLE.

*Farr SL. Contraception. 2010 ;82:64-71
Cullwell KR. Obstet Gynecol. 2009;114:341-53.

RA and Contraception

- H 108 premenopausal RA women sent a questionnaire regarding contraception
- High rates (33%) ineffective contraception (none, abstinence, w/d, rhythm, barrier)
- 22% used "Effective"(eg, hormonal or IUD)
- 45% sterilized
- 56% were on MTX or LEF
  - 28% ineffective; 23% effective; 48% sterile
- 19% used HCQ (19%/ 30%/ 35%)
- 53% used TNFi (40%/ 25%/ 36%)

Clowse ACR 2011

Drugs and Pregnancy

- 62 million F of childbearing age (15-44 yrs) in USA
- ½ of all pregnancies are unintentional
- 90% of pregnant women take ≥1 Rx Meds
  - 50% take ≥4 medS during pregnancy (avg 3-5 drugs)
- >14% Have Comorbidities (asthma, HTN, depression, diabetes, arthritis) often require the same drugs before, during and after pregnancy
- Postpartum Rx exposure (during lactation)common
- Thalidomide heightened concerns about drug exposure risk during pregnancy
- The effects of DMARD or biologic exposures have not been adequately tested

Thalidomide

- 1950s – 1960s to Rx Nausea in pregnant women
  - Never FDA approved/used in USA (neuropathy)
- Proved useful in leprosy and multiple myeloma.
- Approximately 10,000 children born with phocomelia→ ban of thalidomide in 1961.
- Critical exposure period is 24–32d postfertilization
- Thalidomide limb teratogenicity: (1) oxidative stress/damage, (2) DNA intercalation, (3) inhibition of angiogenesis, and (4) Cereblon binding
- System for Thalidomide Education & Prescribing Safety (STEPS) to safeguard against potential exposure of pregnant women

Drug Exposure in RA Pregnancy

- 393 pregnancies among 34,169 US RA women (2002–2008)
- DMARD exposure
  - 24% during preconception
  - 21% during Pregnancy
  - ↓ from 1st to 3rd Trimester (p0.03)
- Spont. Abortions not incr by steroid or TNFi use

90 days before delivery	Drug use	During pregnancy
13.2%	NSAID	11%
32.7%	Prednisone	55.5%
32%	DMARD	22.8%
16.7%	Biologic	12.5%
8.2%	Category X	3.9%

Category X: MTX, LEF, AZA (D)

Prednisone, DMARD & TNFi use is common before / during Pregnancy
Education is needed about drug use in patients planning for pregnancy

Kuriya B, et al. Arthritis Care Res. 2011;63:721-8.

Drug Exposure in RA Pregnancy

- Norway: Among 154,976 pregnancies
- ~1% of mothers (1461) & fathers (1198 received antirheumatic Rx in the 3 mos prior to and/or during pregnancy
- **No Malformations seen in those exposed to MTX, LEF, ETAN, ADA**

Drug exposures

- 723 NSAIDs
- 633 prednisolone
- 119 sulfasalazine
- 101 azathioprine
- 58 hydroxychloroquine
- 37 etanercept
- 8 methotrexate
- 2 leflunomide
- 3 adalumimab

Viktil K. Scand J Rheumatol. 2012 May;41(3):196-201.

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

2011 FDA Guidance Change

- 2011 Proposed changes to Pregnancy & Lactation Labeling
- Dissatisfied with the 1979 category A, B, C, D, X ratings for drug risk to the fetus in preg. “confusing & overly simplistic”
- “to include relevant clinical information to help health care providers make prescribing decisions and counsel women about the use of drugs during pregnancy and/or lactation.”
- To include a concise narrative summarizing a product’s risks to pregnant women. Pregnancy subsection 5 components:
  1. Fetal Risk Summary: contraindications, warnings precautions, developmental
  2. Clinical Considerations section germane to management
  3. Data section: discussion of data underlying risk assesments
  4. Pregnancy exposure registry information (if applicable)
  5. General statement about the background risk of fetal developmental abnormalities.

8.1 Pregnancy
Pregnacy Category B

- **Risk Summary**
  - Adequate and well-controlled studies with CIMZ IA have not been conducted in pregnant women. Certolizumab pegol plasma concentrations obtained from 10 women treated with CIMZIA during pregnancy and their newborn infants demonstrated low placental transfer of certolizumab pegol. CIMZIA may be eliminated at a slower rate in exposed infants than in adult patients. No fetal harm was observed in animal reproduction studies. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to CIMZIA during pregnancy. To enroll, healthcare providers or patients can call 1-877-311-8972.
- **Human Data**
  - In an independent clinical study conducted in 10 pregnant women with Crohn´s disease treated with CIMZIA, certolizumab pegol concentrations were measured in maternal blood as well as in cord and infant blood (n=12) at the day of birth. The last dose of CIMZIA (400 mg for every mother) was given on average 19 days prior to delivery (range 5-42 days). Plasma certolizumab pegol concentrations were <0.41 –1.66 µg/mL in cord blood, <0.41 – 1.58 µg/mL in infant blood, and 1.87–59.57 µg/mL in maternal blood. Plasma certolizumab pegol concentrations were lower (by at least 75%) inthe infants than in mothers suggesting low placental transfer of certolizumab pegol. In one infant, the plasma certolizumab pegol concentrationdeclined from 1.02 to 0.84 µg /mL over 4 weeks suggesting that CIMZIA may be eliminated at a slower rate in infants than adults.
- **Animal Data**
  - Because certolizumab pegol does not cross-react with mouse or rat TNF□, reproduction studies were performed in rats using a rodent anti-murine TNF□pegylated Fab' fragment (cTN3 PF) similar to certolizumab pegol. Reproduction studies have been performed in rats at doses up to 100 mg/kg and have revealed no evidence of impaired fertility or harm to the fetus due to cTN3 PF

Background Risks of Pregnancy

- Varies w/ maternal age & conditions
- 15-20% result in Spont Ab or miscarriage
- 1/200 still birth
- 1/28 infants is born w/serious birth defects
- 3-5% rate of birth defects in gen. population
- Does drug-related risks exceed background risks for adverse outcomes

Federal Register 2008: 73 (104): 30839

Birth Defects During Pregnancy in USA

- 3-5% rate of birth defects in gen. population
- Rates of birth defects:
  - risk in women with epilepsy is 6% to 9%.
  - Acyclovir Pregnancy Registry (1984-1998)
    - 3.3% (19/581)
  - Lamotrigine (antiepileptic Rx) Registry (1992-98)
    - 6.5% (8/123) (CI 3.1%-12.8%)
  - Sumatriptan Pregnancy Registry (1996-October 1998) (7/183), 3.8% (CI, 1.7%-8.0%).

Congenital Anomalies Assoc.with in 452 TNFi Rx Patients with Live Births

Systematic review of 50 references

452 TNFi exposures

Congenital abnormalities (*n* = 19)	Affected	Anti-TNF exposure
Ventricular septal defect	3	IFX, ADA 2
Chromosomal abnormalities	2	IFX
Congenital hip dysplasia	2	IFX , ADA
Intestinal malrotation	1	IFX
Congenital hypothyroidism	1	IFX
Hemangiomas	1	IFX
L hand polydactyly	1	IFX
Tetralogy of Fallot	1	IFX
Patent ductus arteriosus	1	ADA
Atrial septal defect and peripheral pulmonic stenosis	1	ADA
Bicuspid aortic valve and agenesis of corpus callosum	1	ADA
Primary craniosynostosis	1	ADA
Microcephaly	1	ADA
Congenital hydronephrosis	1	ADA
Undescended testes	1	ADA

4.3%

Marchioni RM, Lichtenstein GM. World J Gastroenterol. 2013;19:2591–2602.

VATER & VACTERL

- 2 cases VATER reported by Carter & Vasey
- VACTERL 1.6/10,000 live births (300# in literature)
  - 1st described in 1973: Vert/ trach/ esophageal atresia, cardiac abnl, radial or preaxial limb anomaly
- MEDWATCH Review: TNFi, congenital anomaly
  - 1998-2005→ 41 cases (22 Etan, 19 Inflix, 0 ADA)
  - Most heart defect (4 cong.heart dz, 2 VSD, 2 ASD, 2 great vessel malformations, 1 Tetralogy of Fallot, 1 ventricular hypokinesia); cystic kidney (3), hypospadias (3), teratoma (3), trach stenosis (2), trisomy 21 (2), hydrocele (2). 7 NS
- 24 of the 41 (59%) had a VACTERL-like association – NONE HAD VACTERL

Carter J, Vasey F. ACR 2007 #667

VATER & VACTERL

- Previously reported 1 case VATER (J Rheum 2007)
  - 28yo PsA 25BIW → 50 BIW, taken throughout pregnancy
- New case: ADA Rx who developed tracheomalacia, bronchomalacia, patent ductus arteriosis, a skeletal disorder
- VACTERL 1.6/10,000 live births (300# in literature)
  - 1st described in 1973: Vert/ trach/ esophageal atresia, cardiac abnl, radial or preaxial limb anomaly
- FOI Search FDA Database: TNFi, congenital anomaly
  - 1998-2005→ 41 cases (22 Etan, 19 Inflix, 0 ADA)
  - Most heart defect (4 cong.heart dz, 2 VSD, 2 ASD, 2 great vessel malformations, 1 Tetralogy of Fallot, 1 ventricular hypokinesia); cystic kidney (3), hypospadias (3), teratoma (3), trach stenosis (2), trisomy 21 (2), hydrocele (2). 7 NS
- 24 of the 41 (59%) had a VACTERL-like association – NONE HAD VACTERL

Carter J, Vasey F. ACR 2007 #667

FDA Pregnancy Risk Categories

Preg Cat A	Pregnancy Cat B	Pregnancy Cat C	Pregnancy Cat D	Pregnancy Cat X
	Sulfasalazine	NSAIDs	Azathioprine	Methotrexate
	Etanercept	Glucocorticoids	Mycophenolate	Leflunomide
	Adalimumab	Hydroxychloroquine	NSAID (>32wk)	
	Infliximab	Tofacitinib	Chlorambucil	
	Golimumab	Abatacept	Cyclophosphamide	
	Certolizumab	Tocilizumab		
	Anakinra	Rituximab		
		Cyclosporine		

Category B
Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.

Category C
Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Chambers CD. Arthritis Res Ther. 2006; 8(4): 215.
Østensen M Nat Clin Pract Rheumatol 2005 1: 111–114

FDA and DMARDs

Agent	FDA	Comments
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
Mycophenolate	D	1st trimester Ab; malformations
Cyclosporine	C	
Methotrexate	X	Contraindicated
Leflunomide	X	Minimal human data; contraindicated

Methotrexate – Package Insert

- Methotrexate has been reported to cause fetal death and/or congenital anomalies…not recommended for women of childbearing potential unless there is clear medical benefits > considered risks.
- Pregnant women with PSO or RA should not receive methotrexate.
- T ½ is approximately 3-10 hrs
- Do not start MTX until pregnancy is excluded; counsel pts on the serious risk to the fetus.
- Pregnancy should be avoided if either partner is receiving methotrexate; during and for a minimum of three months after therapy for male patients, and during and for at least one ovulatory cycle after therapy for female patients.
- MTX: embryotoxicity, abortion & fetal defects in humans. Reported to cause infertility, oligospermia and menstrual dysfunction, during and for a short period after MTX cessation

http://dailymed.nlm.nih.gov

Paternal MTX use and Risk for Adverse Pregnancy Outcome

- Prospective Observational Cohort Study
- Paternal use of low dose MTX
- 113 pregnancies with paternal low dose MTX compared to 412 non-exposed
- Rate of major birth defects OR 1.02 (95%CI 0.05-7.0)
- Rate of spontaneous abortion HR 1.19 (95% CI 0.65-2.17)
- Gestational age, birth weight did not differ
- Rate of electively terminated pregnancies higher in MTX exposed patients.

Findings do not support 3 months MTX free interval in males on MTX prior to conceiving.

Rheumatology (Oxford). 2014 Apr;53(4):757-63

Methotrexate

- FDA Category X risk
- Myth: Stop 3 ov. cycles prior to conception (Myth)
- Folic Acid should be continued
- Critical period of exposure is between 6-9 weeks post-conception

- Should MTX pregnancies be terminated??

- WHAT I DO: Counsel pt; NEVER allow MTX use in women planning to get pregnant

Methotrexate Use in Pregnancy

Outcomes	Chakravarty 2002	Donnenfeld 1994	Kozlowski 1990	Lewden 2004	Ostensen 2000	Ostensen 2007
Dose (mg)	Low	7.5-42	7.5-10	10.5	5-15	Low
# Exposed	31	14	8	23	4	1
Miscarriage N (%)	7 (23%)	4 (29%)	3 (38%)	4 (17%)	1 (25%)	1 (100%)
Live births N (%)	23 (74%)	10 (71%)	5 (62%)	19 (83%)	3 (75%)	0
Birth defect N (%)	3 (9%)	1 (7%)	0	1 (4%)	0	0
Total	5/81 = 6.2%					

32 yoF with RA x 6 yrs. Now doing well on Leflunomide x 12 mos. She wishes to become pregnant – what is your advice?

A) D/C LEF for 3 menstrual cycles

B) D/C LEF now and start cholestyramine

C) D/C LEF at the time of conception

D) Reduce LEF 10 mg/d & D/C 1 mo. before conception

Leflunomide Package Insert: Must not be given to:

- Impaired liver function
- Hypersensitivity to Arava
- Severe immunodeficiency; Bone Marrow dysplasia
- Severe uncontrolled infections
- Stevens-Johnson, E. Multiforme, toxic epidermal necrolysis
- **Pregnant or breast feeding women**
- **Women not using reliable contraceptives**
- **Drug elimination:**
  - Administer cholestyramine 8 grams TID x 11d.
  - Verify plasma levels less than 0.02 mg/L (0.02 µg/mL) by two separate tests at least 14 days apart.
  - After 2 days→ 50-65% decrease in plasma levels

Leflunomide

- FDA Category X: embryotoxic & teratogenic
- Drug needs to be eliminated prior to conception (can take 2-3 yrs to excrete)
- Can use Cholestyramine 8g tid x 11d to eliminate prior to conception
- Need serum levels < 0.02mg/L x 2, 2 weeks apart prior to conception
- After cholestyramine, wait three cycles
- OTIS: 64 LEF exposed; 5.4% born w/ defects

Chambers CD. Arthritis Rheum. 2010; 62:1494-503

Nonselective NSAIDs

- 1st trimester: Category B risk
- 3rd trimester: Category D risk
  - Don't use after wk 32: NSAIDs→premature PDA closure=D risk
  - Misoprostil, "Arthrotec" is an abortifacient (X risk)
- Conflicting evidence whether NSAIDs→ Spontaneous abortion
- Reported: implantation issues, cryptorchidism, oral cleft, oligo-hyrdramnios, gastroschisis, cardiac defects, renal insufficiency
- 2 large population (>200,000) pts; 11,787 took NSAIDs without any increased risk of congenital malformation.
- NSAIDs late in pregnancy may cause maternal bleeding, renal insufficiency, low birth wt. in the child. Celecoxib not studied.
- WHAT I DO: NSAID use may be safe between weeks 8 – 32. Remind pts when to stop. No COX-2 NSAIDs, or misoprostil. OK during breastfeeding

BJOG. 2013 Mar 14. J Rheumatol. 2012;39:2163-9

Colchicine

- Am J Obstet Gynecol. 2010 Aug;203(2):144.e1-6. doi: 10.1016/j.ajog.2010.02.063. Epub 2010 Jul 1.
- **Pregnancy outcome after in utero exposure to colchicine.**
- Diav-Citrin O, Shechtman S, Schwartz V, Avgil-Tsadok M, Finkel-Pekarsky V, Wajnberg R, Arnon J, Berkovitch M, Ornoy A.
- **Source**
- Israeli Teratology Information Service and Israel Ministry of Health, Jerusalem, Israel.
- **Abstract**
- **OBJECTIVE:**
- We sought to examine the fetal safety of colchicine.
- **STUDY DESIGN:**
- This was a prospective observational comparative cohort study regarding colchicine exposure during pregnancy including contacts to 2 Teratology Information Services in Israel from 1994 through 2006.
- **RESULTS:**
- In all, 238 colchicine-exposed pregnancies (97.0% first trimester) and 964 pregnancies with nonteratogenic exposure were followed up. Treatment indications were: familial Mediterranean fever (87.3%), Behçet disease (7.5%), or other (5.2%). The rate of major congenital anomalies was comparable between the groups (10/221 [4.5%] vs 35/908 [3.9%]; P = .648). There were no cytogenetic anomalies in the colchicine group. The median gestational age at delivery was earlier (39 [38-40] vs 40 [38-41] weeks; P < .001), the rate of preterm deliveries was higher (32/214 [15.0%] vs 51/867 [5.9%]; P < .001), and the median birthweight was lower (3000 [2688-3300] vs 3300 [2900-3600] g; P < .001) in the colchicine group.
- **CONCLUSION:**
- The present study suggests that colchicine does not appear to be a major human teratogen, and, probably, has no cytogenetic effect.
-
- PMID: 20579964 [

Corticosteroids

- FDA Category C risk
- Low dose (<20mg) considered safe
- High doses
  - Maternal HTN, Gestational Diabetes, Osteoporosis, PROM.
  - ↑ risk of cleft lip +/- palate
- **WHAT I DO:** Try to avoid Steroids if possible
- Use 5-15 mg/d; consider alternatives
  - More likely to use TNFi, HCQ, SSZ, AZA

A 27 y/o woman with well-controlled psoriatic arthritis on low-dose prednisone and sulfasalazine asks if she can continue these medications when she becomes pregnant & breastfeeds her infant.

- Yes
- Psoriatic arthritis does not typically improve during pregnancy
- Prednisone generally safe; a 3-fold increase in cleft lip and palate (the risk increases from 1/1000 to 3/1000)
- Sulfasalazine (SSZ, pregnancy class B) is considered safe during pregnancy and lactation

Clowse M, DSQ 2010

Sulfasalazine

- FDA Category B risk
- 3 large studies in IBD patients (N >300)
- No maternal or fetal toxicity found
  - Men: Causes oligospermia
- **WHAT I DO:** seldom comes up, Counsel on pregnancy planning, OK to continue during; start on daily folate

Azathioprine

- Category D risk
- Reports of 190 babies with IBD or SLE
  - No increased risk of structural defects
  - Noted complications
    - IUGR, cytopenias, Small for gestational age, PROM
  - Increased risk of autism?
- Management: Must do risk/benefit analysis - ?safe if severe underlying dz
- **WHAT I DO:** avoid if possible

Hydroxychloroquine

- FDA Category C risk
- Crosses placenta in humans
- No fetal toxicity in usual doses (6.5mg/kg)
- Multiple case control trials showing no fetal abnormalities
- Considered safe
- **WHAT I DO:** No change in HCQ dosing related to pregnancy

Mycophenolate

- Increased risk of 1st trimester pregnancy loss
- Increased risk of structural abnormalities
- Pregnancy category changed from C to D
- Black Box warning updated 11/07 “pregnancy loss and …. Malformations”

TNFi: Pregnancy is a Relative Contraindication

1. Preg NOT a boxed warning
2. Preg NOT a contraindication

Package insert on TNFi

3. Pregnancy Category B – There are no adequate and well-controlled studies of (TNF Inhibitor) in pregnant women. Because animal reproduction and developmental studies are not always predictive of human response, it is not known whether (TNF inhibitor) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. (TNF Inhibitor) should be used during pregnancy only if clearly needed.
4. Encouraged to enroll such pts with OTIS pregnancy registry 1-877-311-8972

Pregnancy: Effect of RA and ETN,ADA

OTIS Data 2008	ETN	ADA	RA control
n	100	30	53
Live births	94%	90%	87%
Spont. Abort.	6%	10%	9.3%
Major defects	9.4%	9.5%	6.1%

Johnson D I et al ACR 2008 abstr#1387; 1388; Friden C et al ACR 2008 Abst#729; Snoeckx Y et al abstr#702

Notes on Pregnancy and TNFi

- Rat model pregnancy loss from inflammation, uteroplacental perfusion was decreased and survival reversed by maternal Rx w/ IL-10, ETN
- Breast milk and Etanercept use

Concentration (ng/ml) of Etanercept in Maternal Serum, Breast Milk, Umbilical Cord and Child Serum During Breast Feeding										
Days post partum	-7	0	+40	+41	+42	+43	+44	+45	+46	+47
Etanercept, 25 mg s.c	x		x							x
Maternal Serum	640	540	840	1700	1800	2000	1700	1400	1450	1250
Breast Milk			2	3	4	5	3	4	2	<2
Child Serum		40[c]		<4	<4	<4				

[a]Lower detection limit in serum 4 ng/ml. [b]Lower detection limit in breast milk 2 ng/ml.
[c]Blood from umbilical etanercept injection.

J Immunol. 2011;186:1799-808
Rheumatology (Oxford). 2010;49:2225-7.

A 32 y/o woman with RA is on etanercept with good disease control. She wishes to become pregnant and asks if etanercept is safe in pregnancy and lactation.

- (Yes)
- TNFi (class B) do not appear to have any adverse impact on pregnancy success in animal models.
- Few human studies suggest safe use during Preg
- Because many women with RA improve during preg, a trial off of anti-TNF-α therapy may be reasonable
- Stopping 3-4 half-lives before expected delivery may decrease the fetal exposure and risk for infection
- Breastfeeding appears safe, although the recommendation discourage breastfeeding

Clowse M, DSQ 2010

Etanercept

- The concentration of etanercept in cord blood was approximately 1/30th of that in the maternal blood.
- ETN found in breast milk (not child serum)

Concentration (ng/ml) of Etanercept in Maternal Serum, Breast Milk, Umbilical Cord and Child Serum During Breast Feeding										
Days post partum	-7	0	+40	+41	+42	+43	+44	+45	+46	+47
Etanercept, 25 mg s.c	x		x							x
Maternal Serum[a]	640	540	840	1700	1800	2000	1700	1400	1450	1250
Breast Milk[b]			2	3	4	5	3	4	2	<2
Child Serum[a]		40[c]		<4	<4	<4				

[a]Lower detection limit in serum 4 ng/ml. [b]Lower detection limit in breast milk 2 ng/ml.
[c]Blood from umbilical etanercept injection.

J Immunol. 2011;186:1799-808 Rheumatology; 2010;49:2225-7.

Drugs and Breast Milk

Thought to be Safe

- NSAIDs & Acetaminophen
- Corticosteroids
  - < 0.1% of maternal dose
- Antimalarial agents
  - 2% of maternal dose
- Sulfasalazine
  - Undetectable levels in breast milk

Potential Risks

- Azathioprine
  - 0.1% of maternal dose in breastmilk
- Methotrexate
  - Detectable in br. Milk
  - limited data
- Leflunomide – no data
- TNF Inhibitors
  - Small amounts of Etanercept & Infliximab detected in breast milk

Adalimumab

- Pregnancy category B
- Preclinical study show no fetal harm w/ ADA
- “ADA must be used w/ caution in pregnancy”. There is no long-term data regarding effects of adalimumab on the developing fetus.
- Less information on transplacental diffusion
- ADA breast milk < 1/100 of maternal serum.
- ?Rec to stop ADA 8-10wk prior to delivery
  - Reduce placental transport to fetus

Pregnancy Outcome with Adalimumab: The OTIS Project

- Ongoing prospective cohort study, U.S/ Canadian ADA-exposedin 1st trimester
- F/U 1-year postpartum
- Maternal, infant assessments
- External Comparators
- 2004-2012, 312 women enrolled: 69 ADA-exposed

Pregnant Women			
Outcome	ADA Exposed	RA Controls	Healthy Controls
N	69	80	163
Spont Ab	10.1%	7.5%	2.5%
Pre-term	13.6%	18.3%	5.4%
Birth Defects	4.5%	5.2%	6.6%
Infant SIE <1yr	3.3%	2.8%	2.0%

No evidence of excess major or minor malformations in ADA-exposed infants

Chambers, et al. ACR 2012, Washington, #2466

ADA and Pregnancy

- OTIS database: 11/04 0 6/11
- ADA Exposed 161 vs 134 healthy vs RA or CD pts

Table 1: Pregnancy Outcomes of Women in the Cohort Study

Outcome	ADA-exposed RA (N=60)	ADA-exposed CD (N=101)	RA Disease Comparison (N=68)	CD Disease Comparison (N=11)	Healthy Comparison (N=134)
Live born- n (%)	53 (88)	85 (84.2)	62 (91.2)	9 (81.8)	120 (89.6)
Spontaneous Abortion – n (%)	6 (10.0)	13 (12.9)	3 (4.4)	1 (9.1)	2 (1.5)
Therapeutic Termination – n (%)	0	1 (1.0)	0	0	0
Stillbirth – n (%)	0	0	0	0	1 (0.7)
Lost to follow-up – n (%)	1 (1.7)	2 (2.0)	3 (4.4)	1 (9.1)	11 (8.2)
Preterm delivery – n (%)	7 (13.2)	17 (20.0)	11 (17.7)	1 (11.1)	6 (5.0)
Major Malformations – Live born infants – (%)	2/53 (3.8)	11/85 (12.9)	1/62 (3.2)	1/9 (11.1)	5/120 (4.2)
Major Malformations – Live infants – (%)	2/59 (3.4)	14/99 (14.1)	3/65 (4.6)	1/10 (10.0)	5/123 (4.1)

- No evidence of an association between ADA exposure and major birth defects, or a specific pattern of malformation

Johnson DL, ACR 2011, #1874

Certolizumab

- Pregnancy category B
- Fab-PEG -↑1/2 life &↓Placental transp (no Fc)
- Preclinical study show no fetal harm
- PEGanti-TNF Fab' in rats →no impaired fertility or harm to the fetus.
- Less information on transplacental diffusion
- ?Rec to stop ADA 8-10wk prior to delivery
  - Reduce placental transport to fetus

Certolizumab Pregnancies

- CZP is “Fc Free”
  - Placental transfer does not occur
  - By contrast, IFX detected 2-7 mos after birth and Cord/Infant drug levels (ADA, IFX) generally 150-300% of maternal blood levels

Placental Transfer of CZP in Pregnant IBD patients

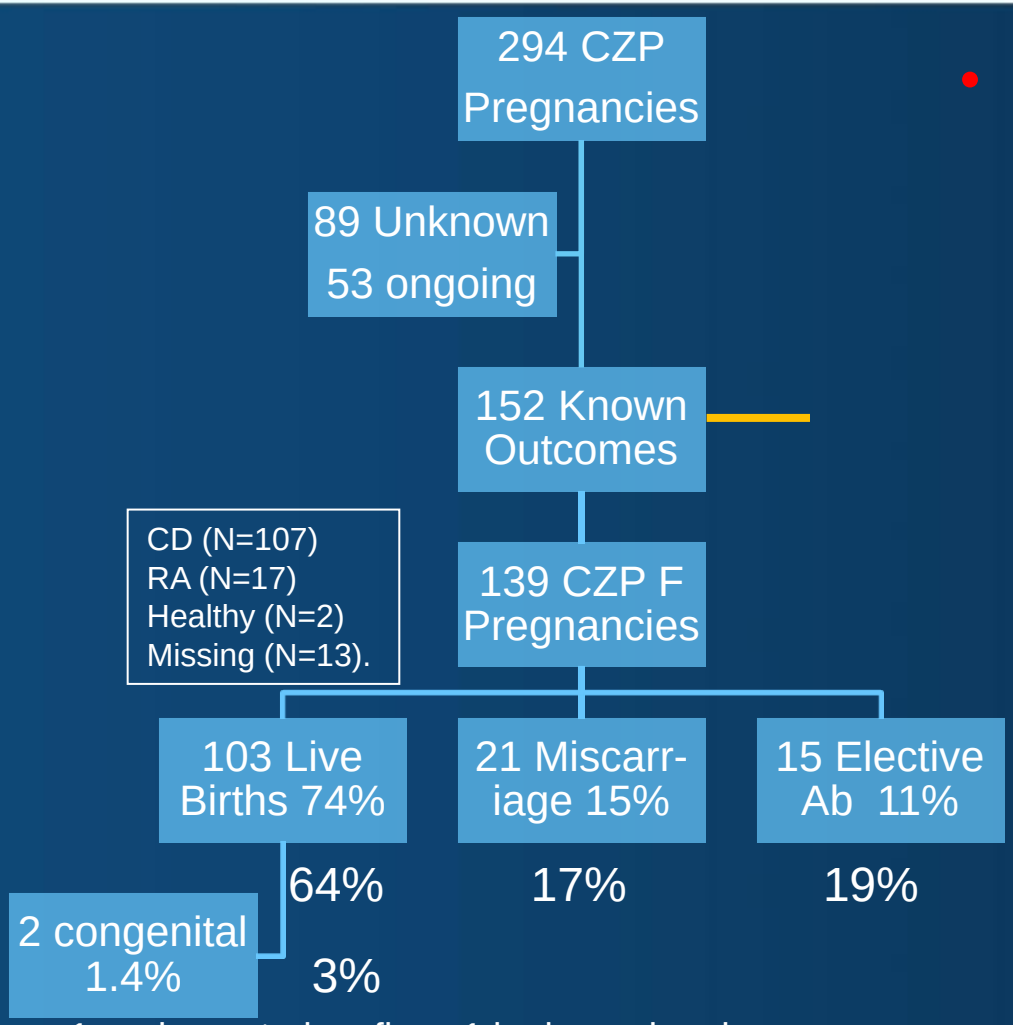
- CZP lacks Fc piece->mediates placental IgG transfer via FcRn
- 31 IBD patients (11 INFL, 10 ADA, 10 CZP) studied prospectv.
- CZP levels in infants & cord blood was < 2 µg/mL

	Infliximab	Adalimumab	Certolizumab
Last dose – delivery (d)	35 (2-91)	38 (1-56)	19 (15-42)
Cord/Maternal Drug ratio	160%	179%	3.9%
Time to clear infant levels	2-7 mos	6-11 wks	NA
Post-partum child events	URI, candida, hand-foot-mouth	Pulmonary edema	none

CZP is not actively transferred via placenta to child

Mahadevan U. Clin Gastroenterol Hepatol. 2013 Mar;11(3):286-92.

Outcomes of Pregnancy in Subjects Exposed to Certolizumab Pegol



Clowse M, et al. ACR 2012, Washington, #1643

- Certolizumab and Pregnancy
  - lack of active neonatal Fc receptor-dependent placental transfer of CZP
  - All pregnancies thru March 2012
  - 57 RCTs + 82 Post-marketing
    + 13 Paternal exposures
    - 10 live, 2 miscarriage. 1 elective Ab
- Miscarriages unrelated to activity

US General Population (National Vital Statistics Data – 1990 to 2004) [3]

CZP Pregnancy Outcomes were consistent w/ that expected from healthy women in the USA

Recommendations

- American Society of Gastroenterology 2006
  - "There is a growing body of evidence suggesting low risk of remicade during pregnancy."
- Reference Center for Teratogenicity of France
  - Use for refractory disease if no other means of control are possible
  - Avoid during final weeks of 3rd trimester
- American College of Rheumatology Recommendations for the Use of DMARDS and Biologic Agents in the Treatment of RA 2012 Update
  - No commentary on use in pregnancy

Bogas M, Leandro M. Biologic therapy and pregnancy. A systematic literature review. Acta Rheumatol Port. 2011 Jul-Sept;36(3):219-232.
Singh J, et al. 2012 Update of the 2008 American College of Rheumatology Recommendations for the Use of Disease-Modifying Antirheumatic Drugs and Biologic Agents in the Treatment of Rheumatoid Arthritis. Arthritis Care & Research Vol. 2012:64(5) 625– 639.

Recommendations

- TNFi placental transfer limited during 1st trimester
- IgG1 subtype of both human and chimeric antibodies readily passes during 2nd and 3rd trimesters
- Conflicting data measuring serum levels in newborns

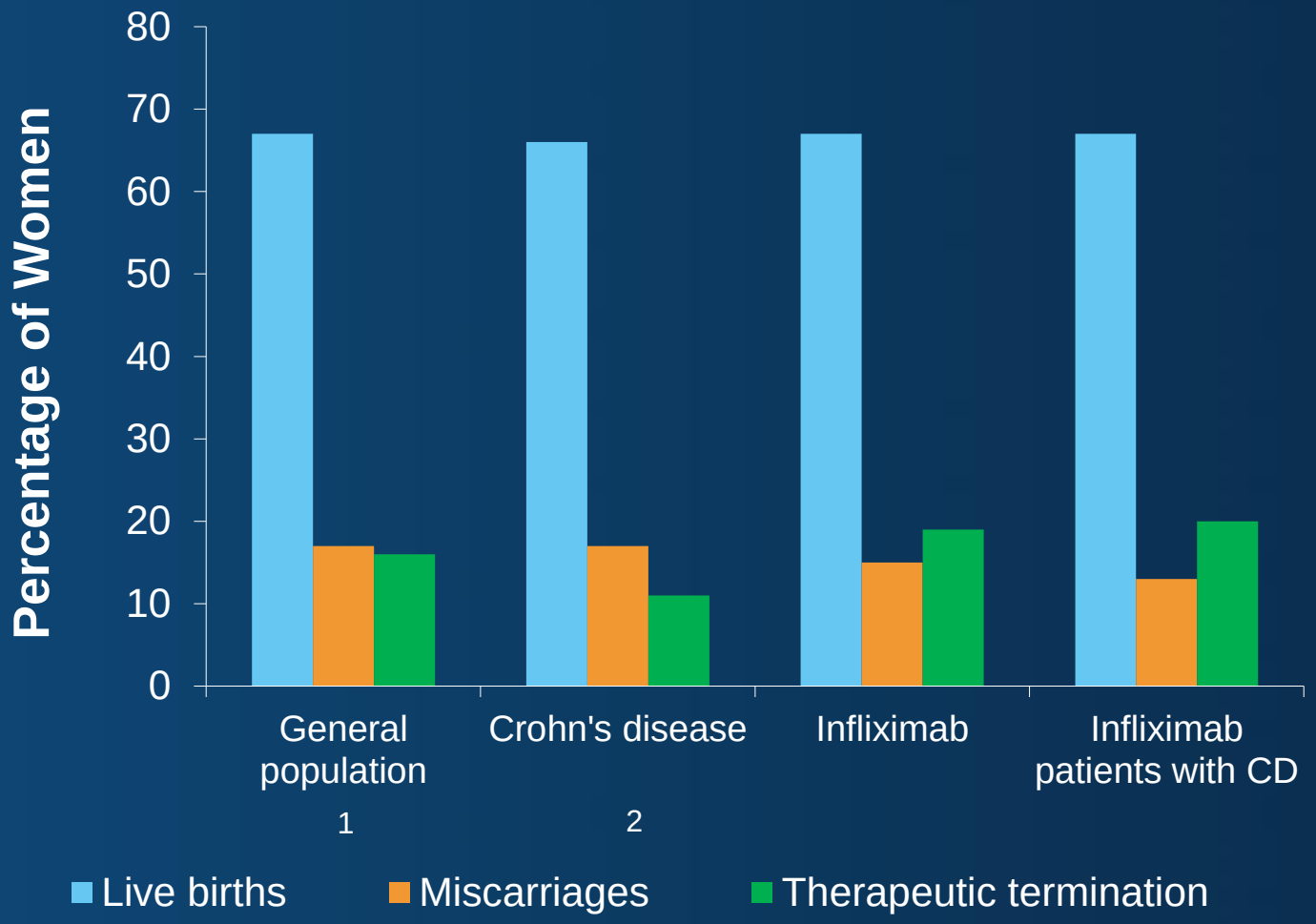
Bogas M, Leandro M. Biologic therapy and pregnancy. A systematic literature review. Acta Rheumatol Port. 2011 Jul-Sept;36(3):219-232.
Ostensen M, Forger F. Treatment with biologics of pregnant patients with rheumatic diseases. Curr Opin Rheumatol 2011; 3:293–298.
Vinet E, et al. Anti-TNF therapy and pregnancy outcomes in women with inflammatory arthritis. Expert Review of Clinical Immunology. 5.1 (2009) 27.

Infliximab Use During Pregnancy

Author	Database Type	N	Disease
Katz et al, 2004	INF Safety DB	96	CD, UC, RA
Lichtenstein et al, 2004	TREAT Registry	36	CD
Mahadevan et al, 2005	Retrospective (intentional use)	10	CD
Chambers et al, 2004	OTIS Study	4	RA
Chambers et al, 2005	Case Reports	8	CD (n=5) RA (n=2) PSA (n=1)
	TOTAL	154	131 women 15 male partner

Katz, JA. *et al. Am J Gastroenterol*. 2004;99:2385-2392.

Infliximab Pregnancy Outcomes



Katz, JA. et al.Am J Gastroenterol. 2004;99:2385-2392. Ventura et al. National Center for Health Statistics Vital Health Stat 2000;21:1-59. Hudson et al. Int J Gynaecol Obstet 1997;58:229-237.

Infliximab

The TREAT Registry in Crohn's & Pregnancy

- A prospective registry of patients with Crohn's Disease
- Patients may or may not be treated with infliximab
- 5,807 patients enrolled
  - 36 patients with prior infliximab exposure

	Prior INF (n=36)	No Prior INF (n=5741)	p Value
Rate of Miscarriage (%)	11.1	7.1	p=0.53
Neonatal Complications (%)	8.3	7.1	P=0.78

Lichtenstein et al, Gastroenterology 2004: 126; A54 (Abstract)

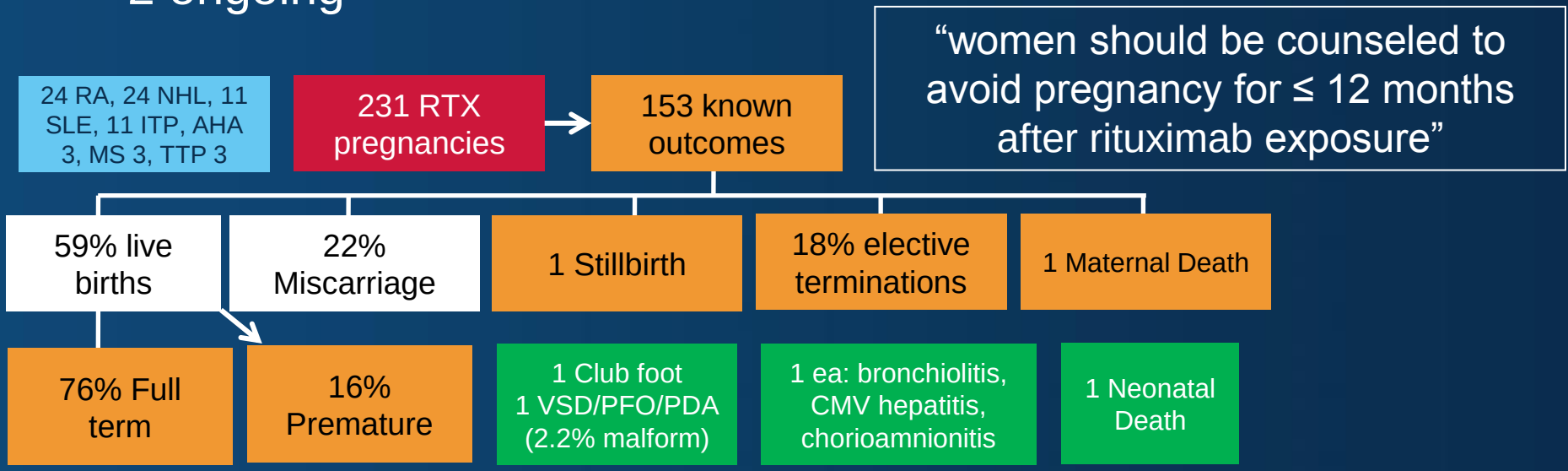
TNF Inhibitors and Pregnancy

- Mabs transplacental passage during Preg.
- Mab concentrations in cord blood similar to or higher than maternal levels at term.
- in-utero infliximab after wk 30 has been shown to result in high blood levels in the newborns.
  - prolonged infliximab half-life in newborns could result infant immunosuppression (live vaccines).
  - Fatal BCG disseminated occurred in a 4.5 mos. infant born to a mother with Crohn's disease
- ↑ TNFα levels been shown w/ miscarriage

2011 Review of RTX Exposed Pregnancies

RTX Global Drug Safety Database

- 231 Pregs: 11 ongoing; 11 paternal; 69 outcomes unknown
- 2 Congenital anomalies (2.2%): club foot and VSD/PFO/PDA
- 4 Neonatal infx: FUO, bronchiolitis, CMV, chorioamnionitis
- 22 Paternal exposures: 11 known- 2 miscarried; 7 live births, 2 ongoing

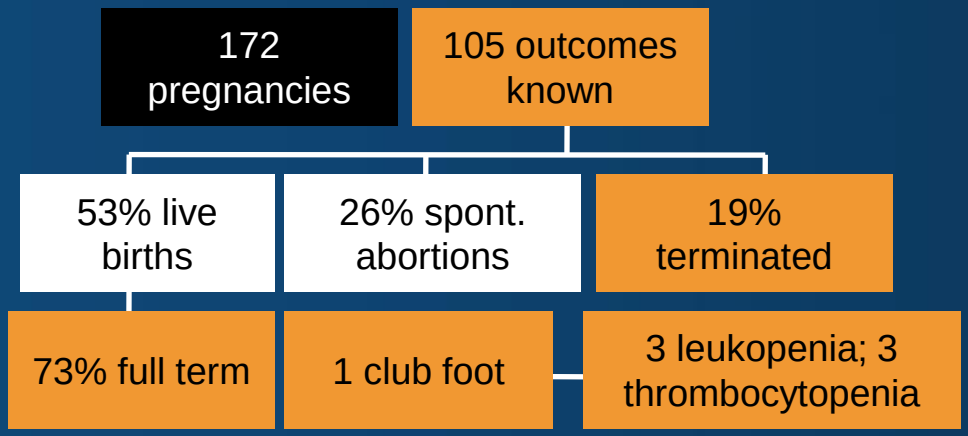


Chakravarty EF, et al. Blood. 2011 Feb 3;117(5):1499-506.

Pregnancy outcomes with RTX, TCZ (C)

RTX Global Drug Safety Database

- 172 pregnancies: 16 ongoing; 11 paternal; 40 no reported outcomes



TCZ Clinical Trial Program

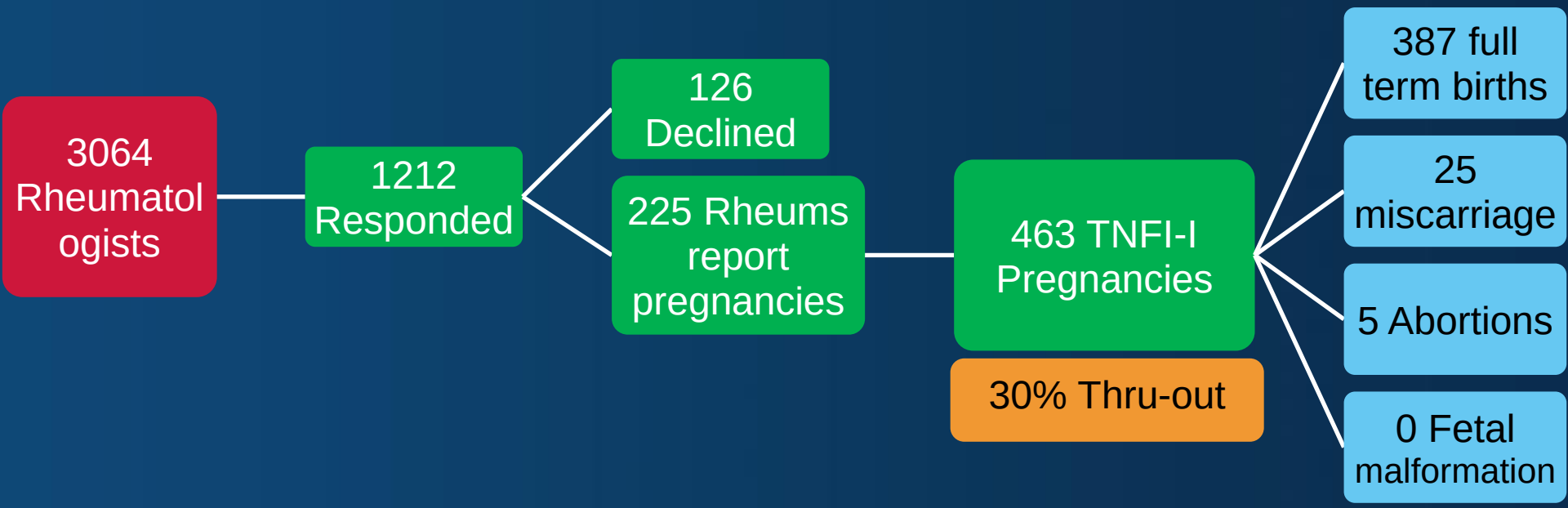
- 38 pregnancies (35 pts) among 4009 pts
- TCZ/MTX stopped w/ pregnancy
- 13 therapeutic and 8 spontaneous abortions
- 14 full-term deliveries: 1 died (ARDS); 1 congenital defect (kidney pelviectasis)

RTX and TCZ are Category C pregnancy risk (may cause fetal harm)
There is too little data to judge their safety in pregnancy

Chakravarty EF, et al. ACR 2010, Atlanta, #401 Rubbert-Roth A, et al. Ibid, #384
Courtesy of TREG Consultants

Safety Of TNF Inhibitors During Pregnancy in Patients With Inflammatory Arthritis

- 3064 rheumatologists (US, Canada) surveyed on the safety of TNF-inhibitors (Cush JJ. Biologics in practice. ACR 872)
- 463 pregnancies on TNF-inhibitors reported by 225 rheumatologists



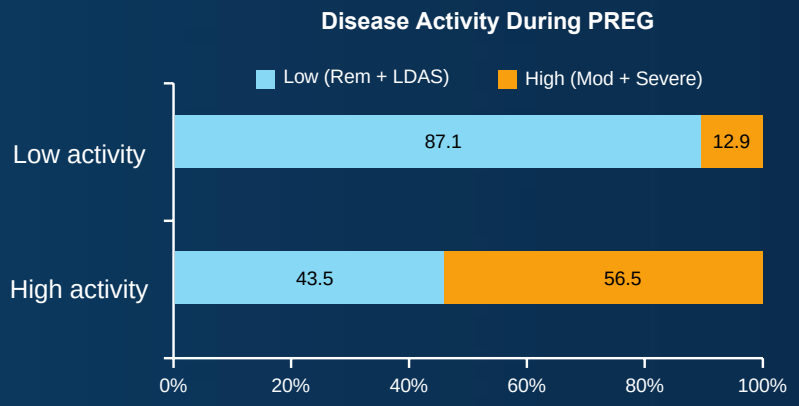
Cush JJ. *Ann Rheum Dis*. 2005 Nov;64 Suppl 4:iv18-23

CORRONA: Pregnancy & TNF inhibitors

- CORRONA: 147 PREG in 38555 RA, PsA
- PREG had low activity & less drug use
- PREG pt more likely to be on TNFi
  - 54% before Pregnancy
  - 27% during Pregnancy
- Low activity before PREG predicted low activity (87%) during PREG.
- High activity before PREG, improved to low activity in only 43% during PREG
- 27% flared, 18% had high disease activity

Low disease activity & deliberate, selective low drug use characterizes PREGNANT pts in CORRONA

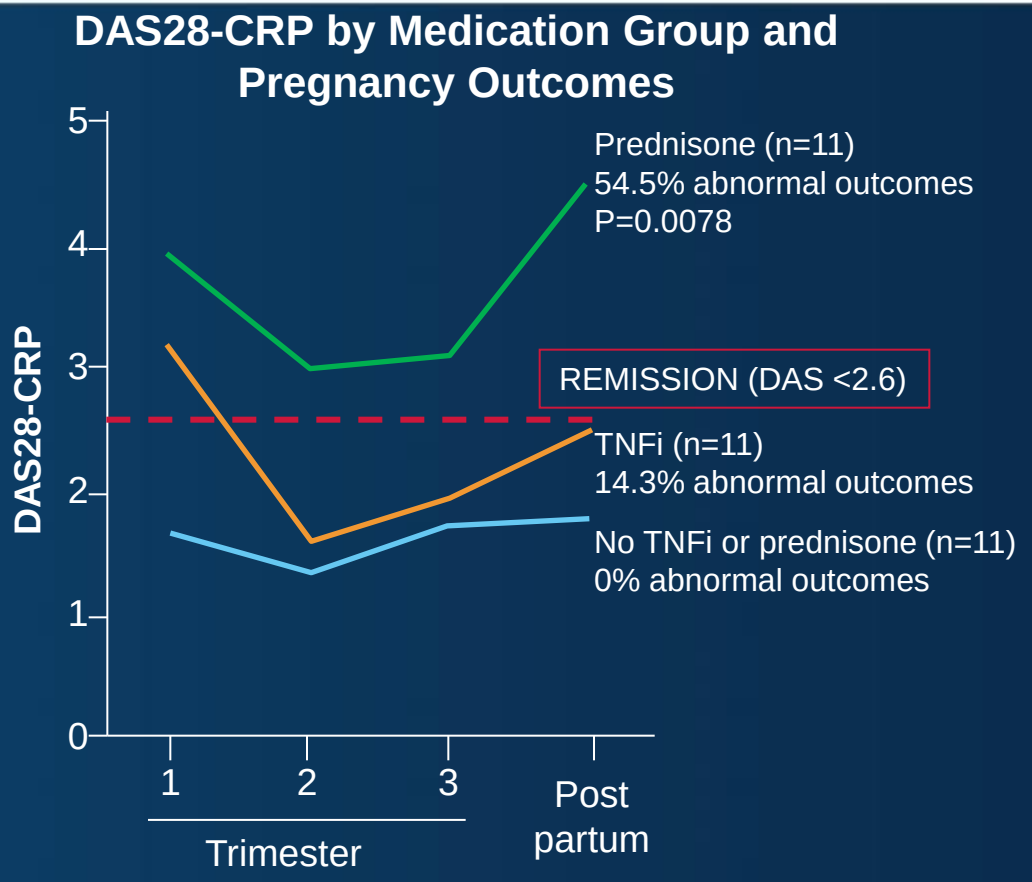
	All CORRONA Females	PRE (Before)	PREG (During)
NSAID	44.8	34	12.2
Prednisone	22.4	23.1	12.2
Pred Dose	7.0	6.2	6.4
MTX	56.6	15.7	4.1
NB-DMARD	73.2	40.1	21.1
TNF inhib	37.6	54.4	27.2
Other Biologic	8.1	4.1	2.0
DMARD free	13.1	37.9	61.2



Cush JJ, et al. ACR 2012, Washington, #389

Prednisone Use Associated with Worse Outcomes in RA Pregnancies

- TNFi use is controversial in pregnancy; prednisone is preferable
- 31 pregnancies: TNFi (29%), prednisone (48.4%)
- Of 29 live births, 5 preterm delivery (17.2%) and 3 pre-eclampsia (10.9%)
- Remission: 1st trimester (54%), 2nd (77%), 3rd (67%), postpartum (61%)
- Strong correlation between DAS-CRP and Patient Global (r=0.86)
- HCQ and SSZ use had even distribution between groups and no impact on pregnancy outcomes



Increased RA activity and prednisone used associated with more preterm birth ± preeclampsia; TNFi may be preferable to prednisone in RA pregnancies

Chaudhary P, et al. ACR 2012, Washington, #1330

CORRONA: OPERA Study

(Outcomes in Pregnancy & the Effects of Rheumatoid Arthritis)

	PRE (n=147)	PREG (n=147)
TJC	2.0	2.2
SJC	2.0	1.9
CDAI	7.8	7.7
GAS	5.9	6.0
Low Activity %	68.9	59.9
High Activity %	31.3	17.8
mHAQ	0.22	0.22
ESR mm/hr	20.5	22.4
MTX %	15.7	4.1
NB DMARD%	40.1	21.1
TNFi %	54.4	27.2
Other Biologics	4.1	2.0
DMARD Free %	37.9	61.2
Prednisone %	23.1	12.2
NSAID %	34.0	12.2

- Likely to have low level disease activity
- Less commonly MTX, NB-DMARD, Pred or NSAIDs
- TNFi were most frequently used pre- & during preg.
- (53% stopped TNFi during PREG)

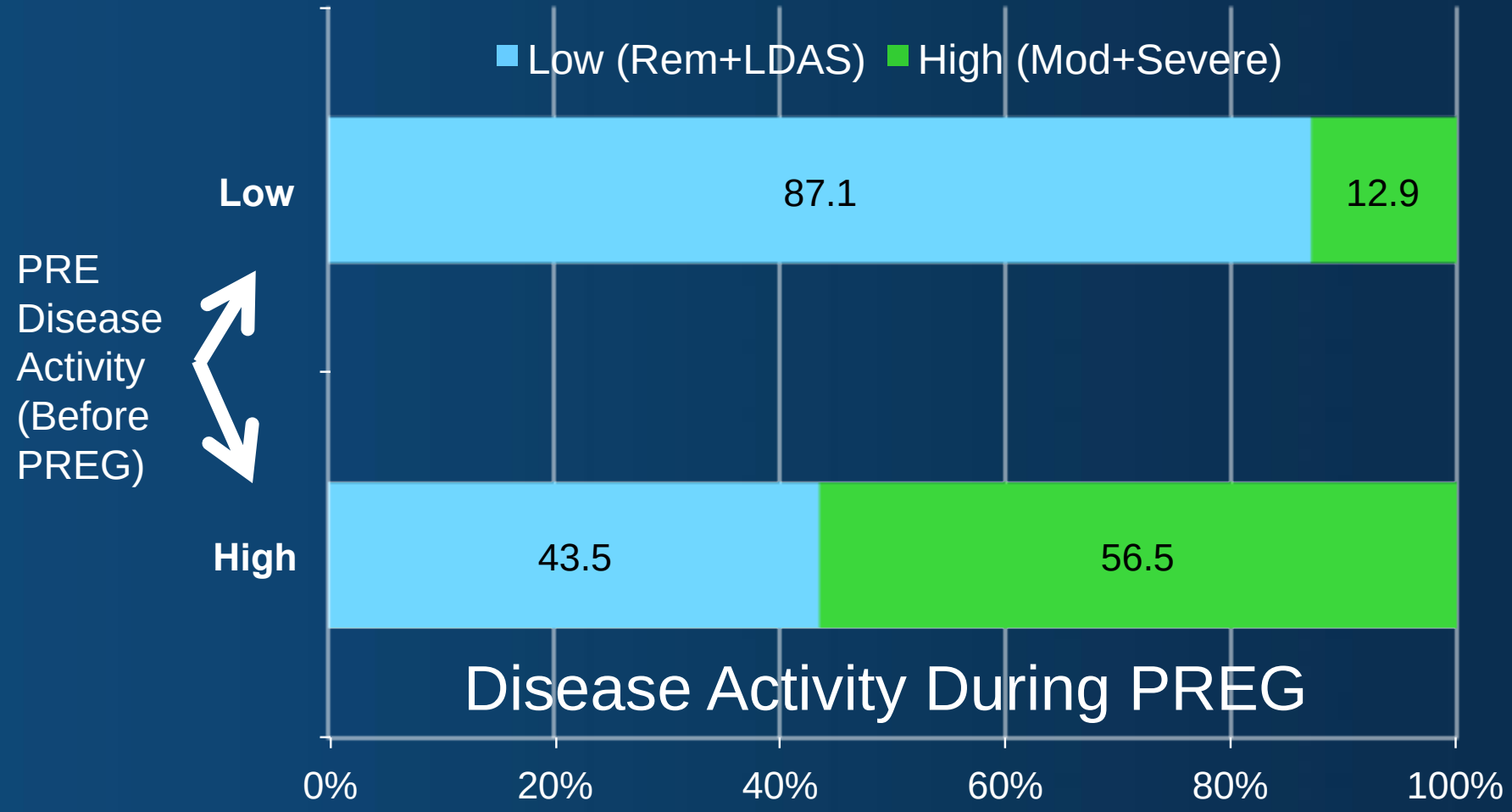
Survey of 600 Rheums: 175 (29%) Respond. Fetal Risk, OCP use, DMARD Outcomes

Table 3. **Number of Pregnancies and Reported Outcomes.**				
	Methotrexate	Leflunomide	Etanercept	**Infliximab**
Total number of pregnancies*	39	10	15	2
Fullterm healthy deliveries, n	21	2	6	1
Congenital malformations (no. deliveries) †	3	0	0	0
Preterm delivery, n	0	1	0	0
Elective abortions, n	8	2	1	0
Spontaneous abortions, n*†	7	1	1	0
Patients still pregnant, n	1	2	4	0
Outcome not stated, n	0	2	3	1

*One pregnancy resulted in spontaneous abortion after exposure to MTX and ET at conception.
† One pregnancy (taking MTX) resulted in a spontaneous abortion; the fetus had a congenital malformation.

Chakravarty E et al, J of Rheum 2003;20:2 p 241-246

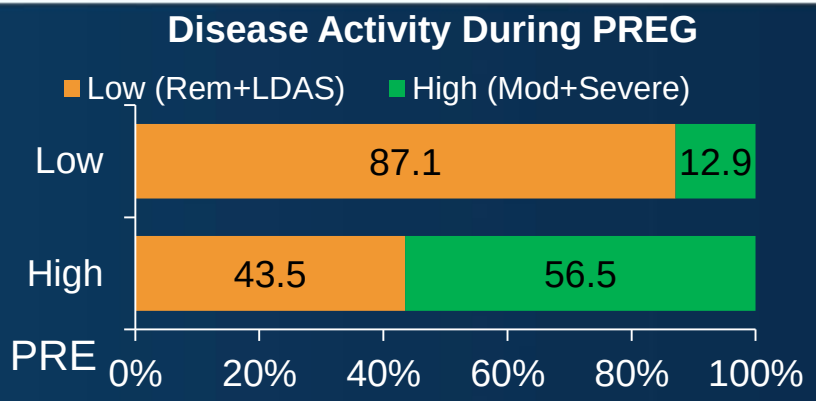
Disease Activity Change from PRE→PREG



Low activity at PRE predicted an 87% chance of Low activity during PREG.
High activity at PRE had 43.5% of improving to Low activity during PREG

Pregnancy and TNF Inhibitors

- **CORRONA** 147 Pregnancies in 5307 women
- PREG pts had low activity & less drug use
- Dz activity before, predicted PREG activity ⇨
- PREG pt more likely to be on TNFi (54%) before & stay on TNFi (27%) during PREG



- Certolizumab (CZP) and Pregnancy exposure
- 139 CZP exposed: 103 Live, 21 SAB, 11 TAB
- Miscarriages not associated with disease activity
- 2 Malformations (3%): vesicoureteric reflux, hydronephrosis

	Live births	Miscarriages	Elective Ab.
CZP	74.1%	15.1%	15.1%
US pop	64.3%	16.1%	19.1%

- OTIS: ADA pregnancy Registry
- n=89, mean age 32 y
- 87% live births; No still births
- 3 defects:VSD,microcephaly, cryptorchidism

Outcome	ADA (69)	RA (80)	Healthy (163)
Spont Ab	10.1%	7.5%	2.5%
Pre-term	13.6%	18.3%	5.4%
Defects	5%	4.2%	6.8%

TNFi use during pregnancy not assoc with higher rates of poor outcomes

Cush JJ, et al. ACR 2012, Washington, #380; Clowse M, et al. ibid, #1643; Chambers, et al. ibid, #2466

Males, Fertility & TNFi

- TNFi (INF, ETN, ADA) studied 26 SpA males
- Sperm abnormalities in TNFi = 102 Control
  TNFi Rx had better sperm motility and vitality
- CZP 13/152 pregnancies had
  Paternal Expos.
- 10 live, 2 miscarriage. 1 elective Ab

TNFi Exposures and Pregnancy

2013 Literature Review of 50 references and total of 472 fetal exposures.

TNFi exposed	Birth Outcomes (%)						
	Fetal exposures	Live births	Spont Abortion	Still Birth	Premature	LowBirth Weight	Congenital anomaly
IFX/ADA/CZP total	472	85.8%	8.2%	0.6%	19.9%	6.1%	4.1%
IFX[1]	194	79.9	10.6	1.1	26.9	4.4	4.0
IFX in IBD[2]	151	77.5	8.9	1.4	36.4	4.8	3.5
ADA[1]	261	92.7	6.9	0	15.9	28.6	5.4
ADA in IBD[2]	224	93.8	5.8	0	17	28.6	5.7
CZP[1]	17	47.1	5.9	0	0	12.5	0
CZP in IBD[2]	17	47.1	5.9	0	0	12.5	0
CZP in RA	139	74	15	0	0	nd	1.4
ADA in RA	69	87	10.1	0	13.6	nd	4.5
General US population[69-73]		64.6%	16.5%	0.6%	12.3%	8.2%	3%

"Although promising overall, there is insufficient evidence to prove absolute safety for use of anti-TNFs during pregnancy given the limitations of available data and lack of RCTs"

Marchioni RM, Lichtenstein GM. World J Gastroenterol. 2013;19:2591–2602.

BSRBR Registry	TNFi Use and Pregnancy			
Rx Exposure @ Conception	TNFi plus MTX or LEF	TNFi	TNFi Prior To	NEVER exposed
#Pregnancies	21	50	59	10
% w/ RA	75%	82%	85%	100%
Mean Age yrs	29.7	34.4	32.6	32.5
Steroid use	29%	34%	41%	30%
Baseline DAS28	6.5	6.1	6.0	5.1
Live Births	48%	64%	78%	100%
Terminations	19%	8%	3%	-
Spontaneous Abortion	33%	24%	17%	10%
Death(uterine/neontl)	0	6%	3%	-
Malformation[#] N(%)	2 (9%)	2 (4%)	0	0

- #congenital dislocation of the hip, pyloric stenosis, winking jaw syndrome, strawberry birth mark
- …promising, but no firm conclusions can be drawn about TNFi safety during pregnancy . Guidelines suggest TNFi should be avoided at the time of conception, cannot yet be changed.

Verstappen, *Ann Rheum Dis* 2011;70:823–826

Pregnancy in Biologics: PIANO Registry

- **PIANO:** prospective cohort study from 30 US IBD centers
  - AZA, 6MP, TNFi exposure during pregnancy
  - Pregnancy evaluations: at enrolment, q trimester, postpartum 4, 9, 12 months
  - n=1115; 896 completed pregnancies randomized to 4 groups

Unexposed (326)	AZA/6MP (204)	TNFi (291)	AZA/TNFi (75)

    - 4% SAB, 5.9% malformations; 75% newborns were breast-fed
  - Overall, no TNFi or Thiopurine Rx related complications in mom or offspring
  - Infant infections only ↑ at 12 mos & only w/CZP excluded (RR 1.35; 1.01, 1.80)
  - UC (higher Dz activity): ↑ any complication, pre-term, ↓ birth weight, NICU
  - Sig. ↑ risk SAB (RR 2.6–4.9), C-sect. (1.2) in TNFi & ↑ risk preterm in AZA/TNFi (1.8)

Biologic use during pregnancy has little/no effect on outcomes

Mahadevan U. DDW 2012

Recommendations

- Gravid women require counseling at time of dx; Re DMARD selection, pregnancy planning, Do/Don’ts, Safe/Dangerous, etc
- If child-bearing potential, order pregnancy tests B-HCG, before starting any class D, X
- OCP use MUST be reviewed
- While its smart to limit Rx use during pregnancy, uncontrolled dz is hazardous
  - Liberal use of Acetaminophen, NSAIDs, Pred., HCQ, TNF inhibitors


THE ROANOKE TIMES
Monday, September 20, 2004

STEPHANIE KLEIN-DAVIS | The Roanoke Times

Mellisa Williamson, 35, a Bullitt Avenue resident, worries about the effect on her unborn child from the sound of jackhammers.

What worries you?

TNF-Inhibitors and Infertility

- Th1 cytokines (TNF, IFNγ) Th2 cytokine (IL-10) linked to infertility and recurrent spontaneous abortion (RSA).
- A study[9] of 75 women with previous reproductive failure after in-vitro fertilization (IVF) with high Th1/Th2 cytokine ratios showed successful pregnancy outcomes in 47 women who received adalimumab alone or a combination of adalimumab and intravenous immunoglobulin

Clark DA. J Reprod Immunol. 2010 May; 85(1):15-24.
Winger E. Am J Reprod Immunol 2009; 61:113–120.

TNF-Inhibitors and Infertility

- Editorial: Wallace D, Weissman M. J Rheumatol 2003
  - 50→70% of all conceptions fail; recurrent loss 1-3% couples
- Maternal Tolerance; ? Th2 biased response
  - ? role of complement inhibitory proteins, maternal regulatory T cells, immunoregulatory cytokines in placental milieu
- ? Role of innate immune system in pregnancy loss
  - TNF inhibition improves pregnancy outcomes in antiphospholipid antibody treated mice
- In animal models, immune driven systemic inflammation → ovarian failure/insufficiency → pregnancy loss

Salmon JE, J Clin Invest 2004;114:15-17
Berman J, J Immunol 2004;174:485-90
Erlebacher A, et al. J Clin Invest 2004;114:39-48

Effect of Pregnancy on RA

- Does prior pregnancy affect RA risk/severity
  - Multiparous vs nulliparous and RA risk?
- Does RA have an onset during pregnancy
  - Rare
- Do women with RA have normal # children
  - Reduced in some
- Does RA affect fertility, conception
- Does pregnancy make RA better or worse
- Difference between planned and unplanned ND

Pregnancy in USA

- Approximately 10 percent of women between the ages of 15 and 44 become pregnant annually.
- ½ of all pregnancies in the USA are unintended – hence inadvertent drug exposure during pregnancy is common
- Comorbidities (asthma, HTN, depression, diabetes, arthritis) often require the same drugs before, during and after pregnancy
- Women take average 3-5 drugs during pregnancy
- The thalidomide story has heightened concerns about drug exposure risk during pregnancy
- Postpartum drug exposure (during lactation) is common

Biologics and FDA

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

Roles of TNF & TNFi in Fetal Development

- TNF (animal data)
  - Peripheral lymphoid tissue development
  - Regulation of cell proliferation
  - Immunological pregnancy loss
  - Prevention of birth of offspring with structural anomalies

- Preclinical Studies of Animal Development and TNF-i
  - At high doses (>200x human doses), adalimumab had no evidence of maternal, embryonic toxicity or teratogenicity
  - Etanercept had no effect on maternal mortality, abortion rate, embryo/fetal mortality, fetal gender, weight or appearance and placental morphology
  - Etanercept had no effect on gestational length, parturition, litter size, or number of pups per litter
  - It is unknown if TNF-i are excreted in breast milk