The Use of DMARDs, Biologicals And Other Novel Agents During Pregnancy
Feng Pao Hsii Lecture

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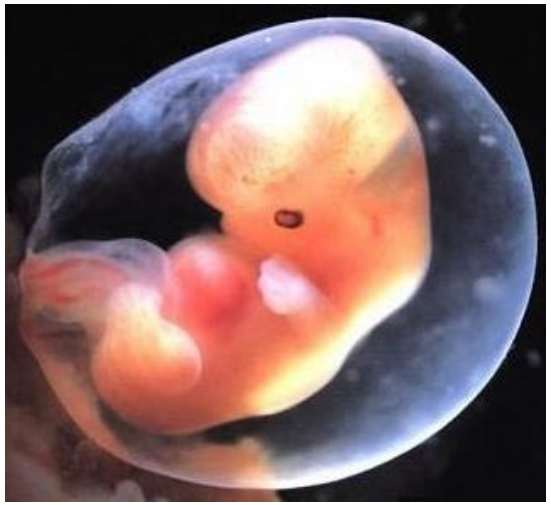
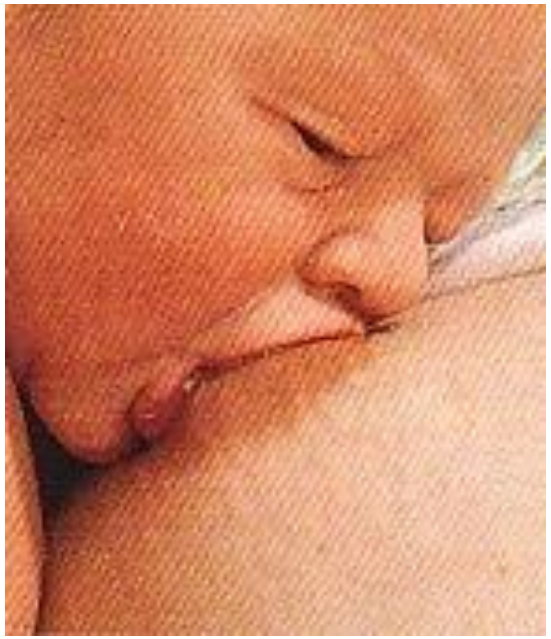




A major concern: Drugs in pregnancy and lactation

Managing pregnant patients with rheumatic disease

- During pregnancy we treat 2 individuals and must care for them both
  - A diseased mother and her healthy child
- Therapy during pregnancy must have a clear indication: treatment of a flare or maintenance of remission

- Aim is to balance between the risk of untreated maternal disease and any possible risk of drugs for the child

The key question

What is the risk of uncontrolled maternal disease for

The mother’s health?

For progression of disease?

For pregnancy complications?

For child outcome?

What is the risk of drug treatment for the fetus/child?

Birth defects?

Impairment of physical and mental development?

Adverse long-term effects?

Pre-conceptional adjustment of therapy

- **Continue** pregnancy compatible drugs that support a healthy pregnancy and a healthy baby

- **Discontinue** teratogenic drugs or drugs with insufficient pregnancy experience where safety for the fetus is not known

Østensen M. Curr Op Rheumatol 2014

DMARDs in arthritis pregnancy

Pregnancy compatible DMARDs	Comment
Sulfasalazine	Belongs to the folate antagonists. **Folate supplementation** necessary during therapy
Chloroquine, hydroxychloroquine	Keep dose of chloroquine at 250mg/day or hydroxychloroquine 5 mg/kg/day
Prednisone	Increases preterm delivery, Keep dose below 10 mg/day
DMARDs to be avoided	**Insufficient knowledge or teratogenic**
Leflunomide	>200 pregnancies: no increase in malformation rate after 1. trimester exposure – no indication that Leflunomid is a human teratogen, but caution needed
Tofacitinib, Baricitinib	Tofacitinib: data insufficient; Baricitinib: no data, avoid
Methotrexate, Cyclophosphamide	Teratogens, stop before pregnancy

Flint et al. Rheumatology 2016; Skorpen et al. ARD 2016

Case 1: Exposure to methotrexate (MTX) at the 1. trimester

- 29 year old woman with RA has been successfully treated with 20 mg MTX/weekly. At start of therapy the necessity of birth control has been discussed with the patient.
- 10 months later the patient phones and tells her rheumatologist that she is 7 weeks pregnant and that she has taken the last dose of MTX at week 6.
- What to do now?

Inadvertant pregnancy exposure to MTX

- Increased rate of congenital malformations at MTX exposure between gestational week 5-8.
- Critical dose of MTX: unknown.
- Malformation rate after once weekly MTX in 1. Trim. is 5-10%
- How to proceed? Refer patient to detailed ultrasound assessment of fetus at week 11-13, repeat at week 17-18
- Shared decision making with the patient according to findings

MTX before and during pregnancy

- **Preconception exposure**
- 136 exposed 0-10 weeks before conception
- Spontaneous abortion 14.4%

- Four children (3.5%) with malformations – no difference to controls

- MTX in 1st trimester
- 188 pregnancies exposed to MTX mean 10 mg/week in 1. trimester
- Rate of spontaneous abortion 42.5%
- Rate of major birth defects 6.6% vs 2.9% in healthy women and 3.5% in disease-matched women

Weber-Schoendorfer et al. Arthritis Rheum 2014

Case 2: a pregnant patient with new onset RA

- A patient with an 8 weeks history of small joint arthritis in hands and feet. Laboratory tests: positivity for rheumatoid factor and for anti-citrullinated protein antibodies (ACPA), DAS 5.8. Takes Diclofenac 75 mg x 2/day. Early MCP erosions on ultrasound.
- Meets with a positive pregnancy test; ultrasound scan shows 8 weeks gestation.

Case 2: How to treat this patient?

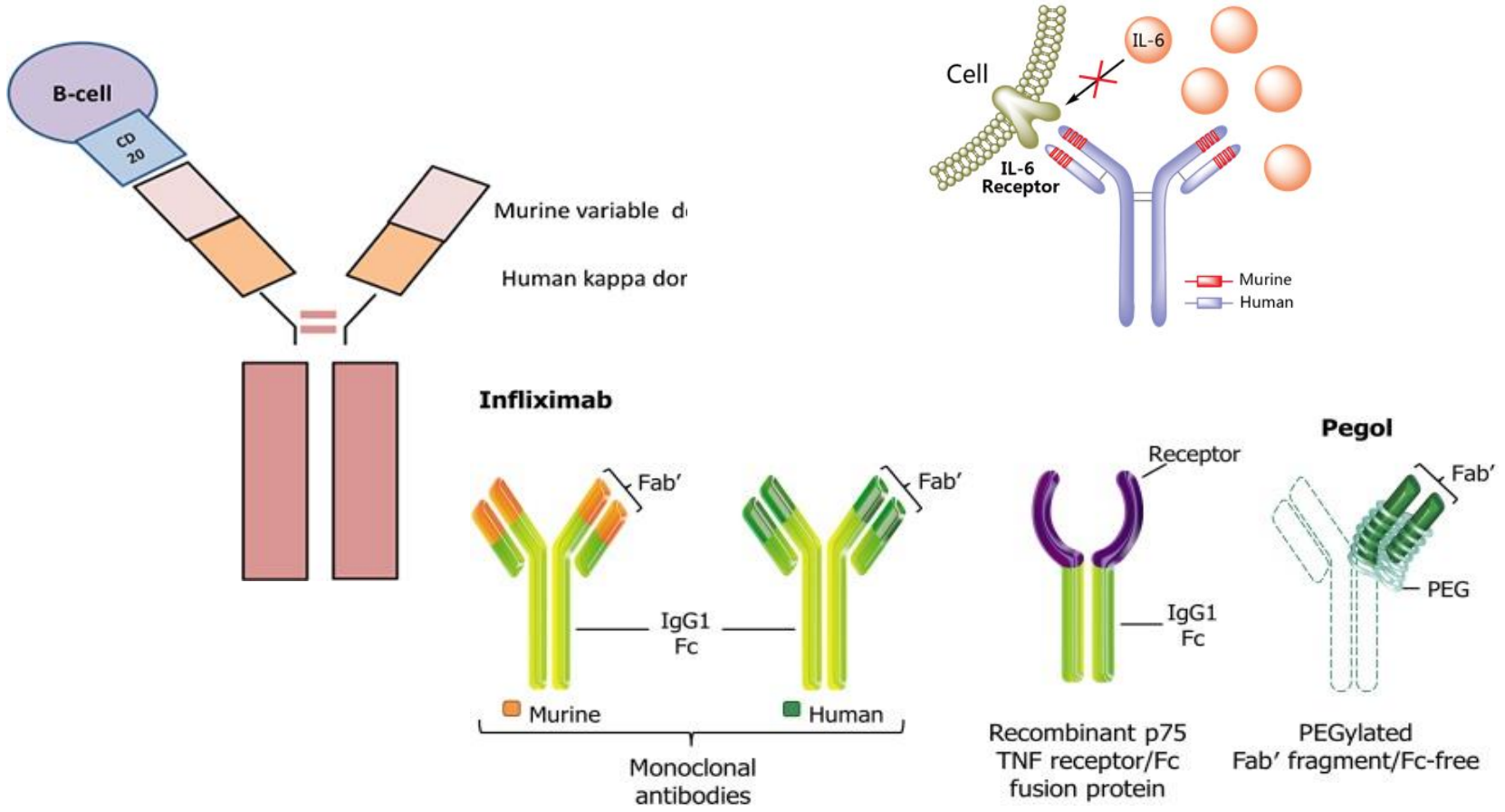
- *With classical pregnancy compatible DMARDs in monotherapy or combination?*
  - No – classical DMARDs need at least 2-3 months to show efficacy. This is too long in a patient with predictors of active and progressive disease who is already 8 wks pregnant.
- *With high dose prednisone alone?*
  - No – in a patient with active polyarticular RA doses exceeding 10 mg/day would be needed for a prolonged period.
- Corticosteroids can be used for achieving a quick mitigation of symptoms and as a bridge while awaiting full effect of other therapy.

May the patient continue Diclofenac, a Nonsteroidal antiinflammatory drug ?

- **Yes, with caution**: No increased risk of congenital malformations shown for non-selective COX inhibitors
- Fetal effects at full anti-inflammatory dose: Constriction of the fetal ductus arteriosus → pulmonary hypertension

- Impairment of fetal renal function
  - Oligohydramnios
- Side effects occur in 2. and 3rd trimester, are **dose dependent** and **reversible** after discontinuation of maternal treatment

Other options: Biologics in pregnancy



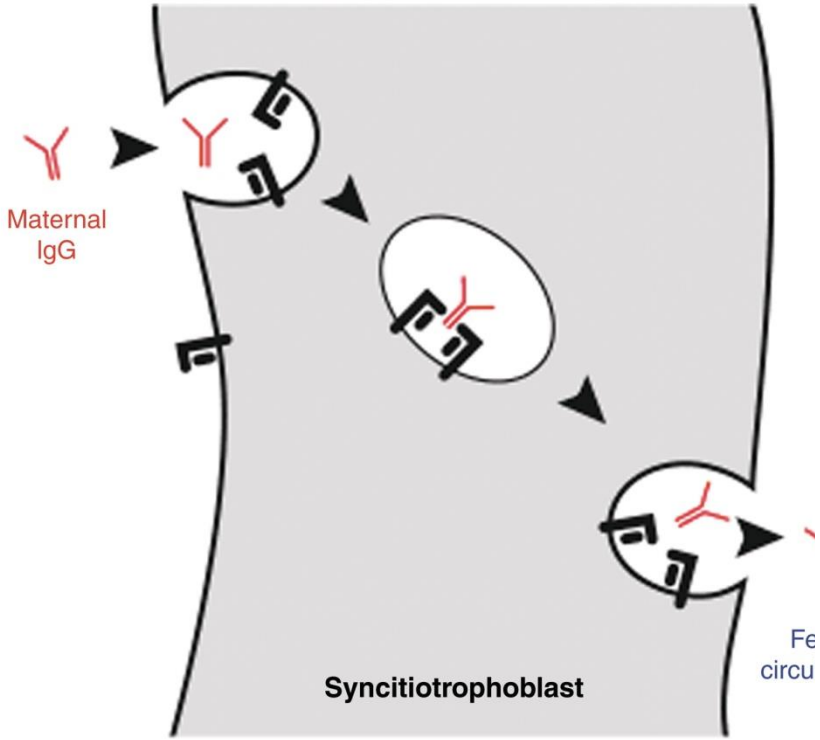
Biologicals in pregnancy- basics

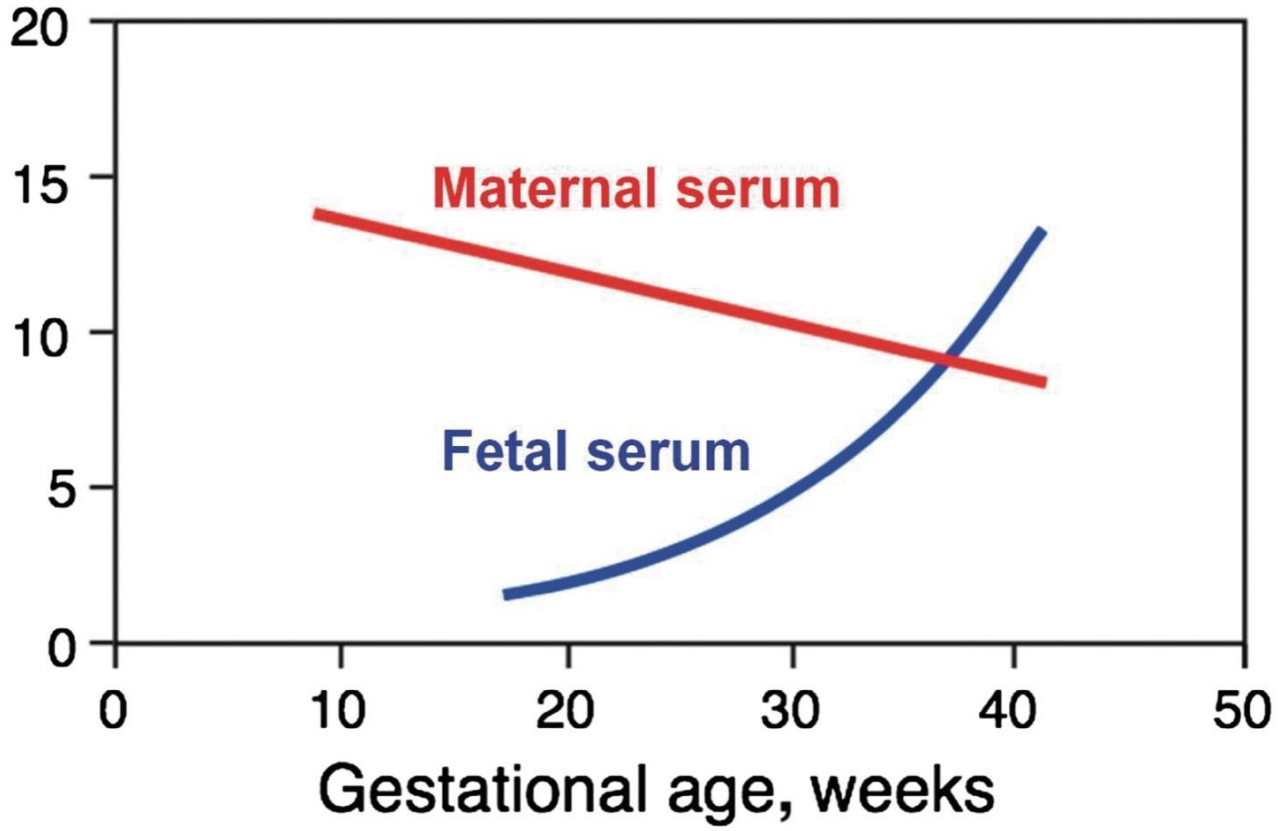
Ssuzuki et aSSSSSSASSSuzuki et al. J Immunol 2010uzuki T, et al. J Immunol 2010; 184:1

Most biologics are IgG1 related molecules, either complete IgG1 or fusion proteins containing the Fc part of IgG1

Transplacental passage dependent on structure, halflife, affinity to fetal Fc-receptor.

Biologics that are complete IgG1 molecules are actively transported through the placenta





Placenta passage of complete IgG1 biologics to the child when given in the 3rd trimester

Drug	Number mother/child pairs studied	Ratio cord blood:maternal blood
Infliximab	97	2.2
Adalimumab	72	1.1
Rituximab	3	1.7
Ustekinumab	3	1.8
Canakinumab	1	2.1

Østensen M. Exp OP Pharmacol 2017

Case 2 contn: Start a TNFi in pregnancy?

- Risk assessment of the pregnant patient with newly diagnosed RA shows **predictors for progressive disease**: presence of rheumatoid factor and ACPA, high disease activity, polyarthritis in hands and feet, early erosions in several finger joints.

- Clinical symptoms support to start a **TNFi with low placenta passage** combined with low dose prednisone.

TNF inhibitors in pregnancy publications and transplacental passage

Drug	Structure	Number pregnancies studied	Ratio cord serum/ maternal concentration
Infliximab (INF)	IgG1 molecule	>1000	2.2
Golimumab	IgG1 molecule	Case reports	1.2
Adalimumab (ADA)	IgG1 molecule	>500	1.1
Certolizumab	Pegylated Fab fragment	>500	0.04
Etanercept (ETA)	Fusion protein with Fc region	>500	0.06
Biosimilars of INF, ADA, ETA		No data	No data

Pregnancy outcome after TNFi exposure

- A meta-analysis of > 1200 pregnancies studied pregnancy outcomes in IBD and RA pregnancies exposed to different TNF inhibitors (TNFi):

- No difference in outcomes miscarriage, preterm delivery, SGA children or congenital malformations when TNFi exposed pregnancies were compared to disease matched controls

Komaki F et al. J Autoimmun 2017

TNF inhibitors and children

- Half-life of monoclonal TNFi prolonged in newborns. Measurable levels of INF and ADA detected in children exposed in late 3rd trimester up to 7-12 months Julsgaard M et al. Gastroenterology 2016

- 380 children, thereof 109 after 3rd trimester exposure toTNFi: no increase in serious infection during the first year of life. Data confirmed by other studies. Vinet E et al. Arthr Rheum 2018

  Chaparro M et al. Am J Gastroenterol 2017; Luu M. et al Am J Gastroenterol 2018

Long term safety of TNFi in pregnancy exposed children

- 4-5 yrs follow-up of 388 exposed and 453 non-exposed children of women with IBD:
- Outcome: severe infection leading to hospitalisation of child
- Result: No increase of serious infection neither with TNFi monotherapy or combination with AZA or mercaptopurine

Chaparro et al. Am J Gastroent 2018; Mahadevan U et al, abstract 2016, Juulsgaard et al. 2016

Vaccination of children exposed during pregnancy

Children should receive inactivated vaccines – follow approved national schedules of vaccination including Hepatitis B vaccine

Children exposed to biologics in utero should wait for 6 months after the mother did receive the last dose before they are given **live vaccines**: rotavirus or BCG vaccine

Vaccination response in TNFi exposed children

- Vaccination responses to inactivated vaccines are normal
- 71 of children followed after exposure to anti-TNF therapy in pregnancy inadvertently got rotavirus vaccine, but had no adverse effects even with very high drug levels

Beaulieu et al. Clin gastroenterol Hepatol 2017 ; Bortlik et al. Inflamm Bow Dis 2014; Sheibani et al. Dig Dis Sci 2015

Patient cases

- Stop the TNF inhibitor during first trimester?
- Continue the TNF inhibitor throughout pregnancy?
- Stop the TNF inhibitor when in remission during pregnancy?
- Patients refractory to standard therapy

A patient with ankylosing spondylitis stops therapy

- 26 yrs old woman with AS for 4 years. In remission on MTX+ adalimumab (ADA). Patient discontinued ADA + MTX a few weeks before a planned pregnancy. No medication until gestational week 7-9, flare responded to 12.5 mg prednisone. New severe flare week 15 that did not respond to 12.5 mg prednisone. Patient totally disabled.
- Question: restart of ADA or change to a TNFi with low placenta passage? *I would not change a drug proven effective*
-

Continue TNFi throughout pregnancy?

- Discontinuation of TNFi in the 1st trimester often results in a flare and necessity to restart TNFi in the 2nd or 3rd trimester

van den Brandt et al. Arthr Res Ther 2017; Berman et al. J Rheumatol 2018; Luu et al. Am J Gastroenterol 2018

- Higher rate of peri-partum and postpartum flare when TNFi are stopped in pregnancy

Genest et al. J Rheumatol 2018

Stop the TNFi when in remission during pregnancy?

- A 33 year old patient with RA has been for 2 yrs in remission on Etanercept 50mg/week

- Takes contact 9 weeks pregnant, normal laboratory and still in remission: Should she stop Etanercept now?

Stop TNFi when the disease is in remission?

There are different options, target: **sustain remission**

- 1. Reduce dose of TNFi by lengthening the interval of injection
- 2. Continue at the same dose of TNFi throughout pregnancy
  - For example in a patient whose disease has been difficult to control
- 3. Stop TNFi and hope the best

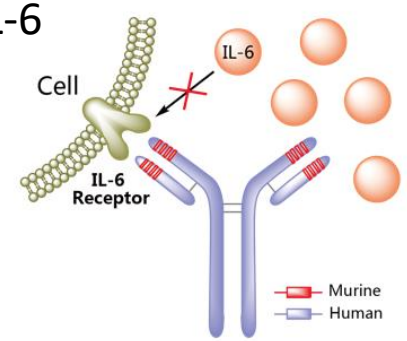
Medications with insufficient pregnancy experience

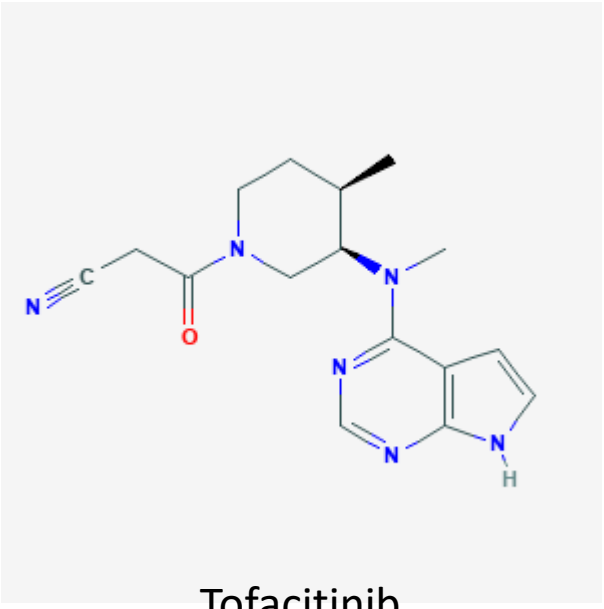
- May one consider drugs with insufficient pregnancy experience in patients with severe, refractory disease?

- Non-TNF biologics

- Targeted molecules

Anti-IL-6





Tofacitinib

Other biologics

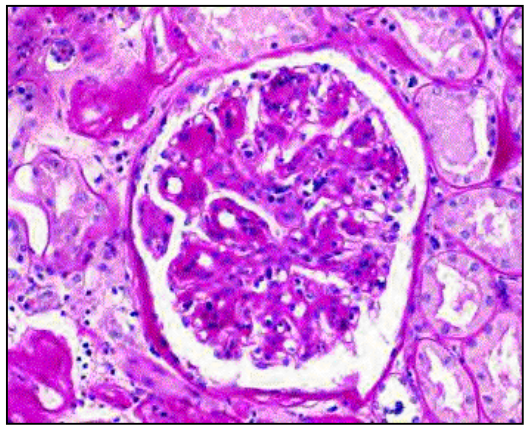
Biologic	Number of pregnancies	Pregnancy outcome	Effect on child	Comments
Tocilizumab Global safety data base and cases	368	Life birth rate 60% High rate of terminations	6 birth defects, no pattern	Most 1. Trim exposures, low placenta passage
Ustekinumab	63	No increase in spontaneous abortion	No birth defects	Preconception/ 1. Trim exposed
Secukinumab Warren et al. Br J Dermatol 2018	119	Spont abortions 11% terminations: 15%	1.9% birth defects	Most 1. Trim exposures
Anakinra	62 cases, mostly AOSD	Normal	2 renal agenesis	Treatment throughout pregnancy. Renal malformation due to AOSD?

Data still insufficient though no danger signals apparent. Use any of these biologics only if no other effective drug can control maternal disease.

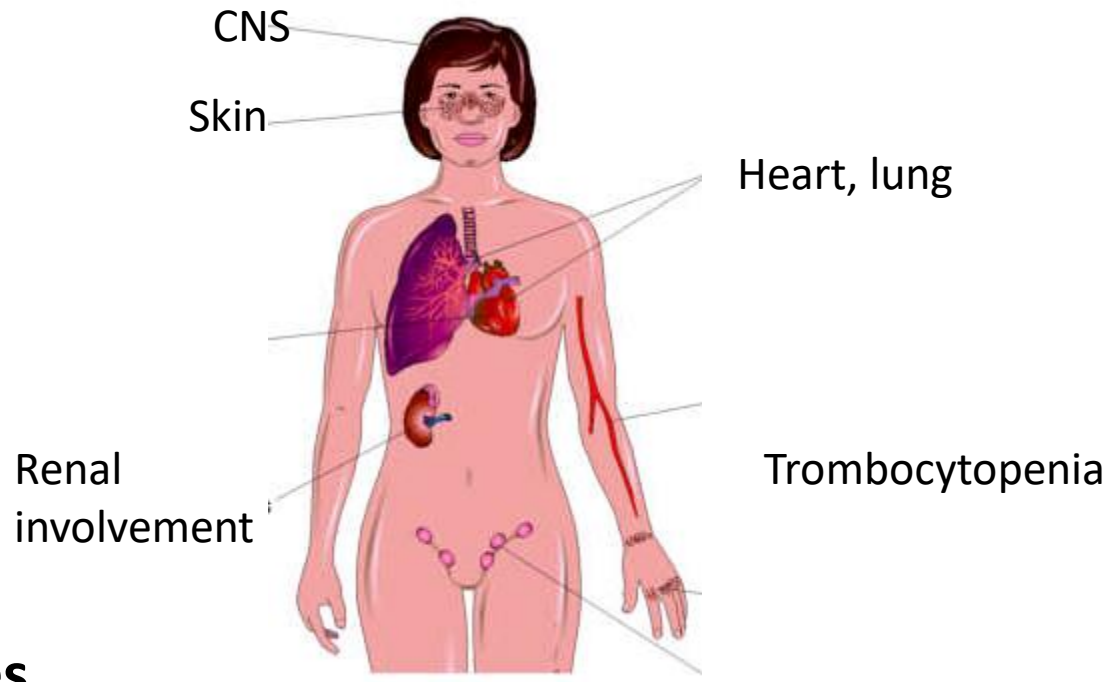
Targeted molecules

- Apremilast: inhibitor of phosphodiesterase 4, used for treatment of psoriasis and psoriatic arthritis
  - Highly limited human pregnancy data, no statement on safety can be made
- JAK inhibitors:
  - Tofacitinib: until 2017, 74 pregnancies reported: no increase of miscarriage or birth defects
  - Baricitinib: Highly limited human pregnancy data, no statement on safety can be made

Managing pregnancies in women with CTD or vasculitis



Patient with
lupus nephritis



CTD and vasculitis are multiorgan diseases, control of disease activity necessary for maternal health and successful pregnancy outcome

Side effects of Corticosteroids (Cs)

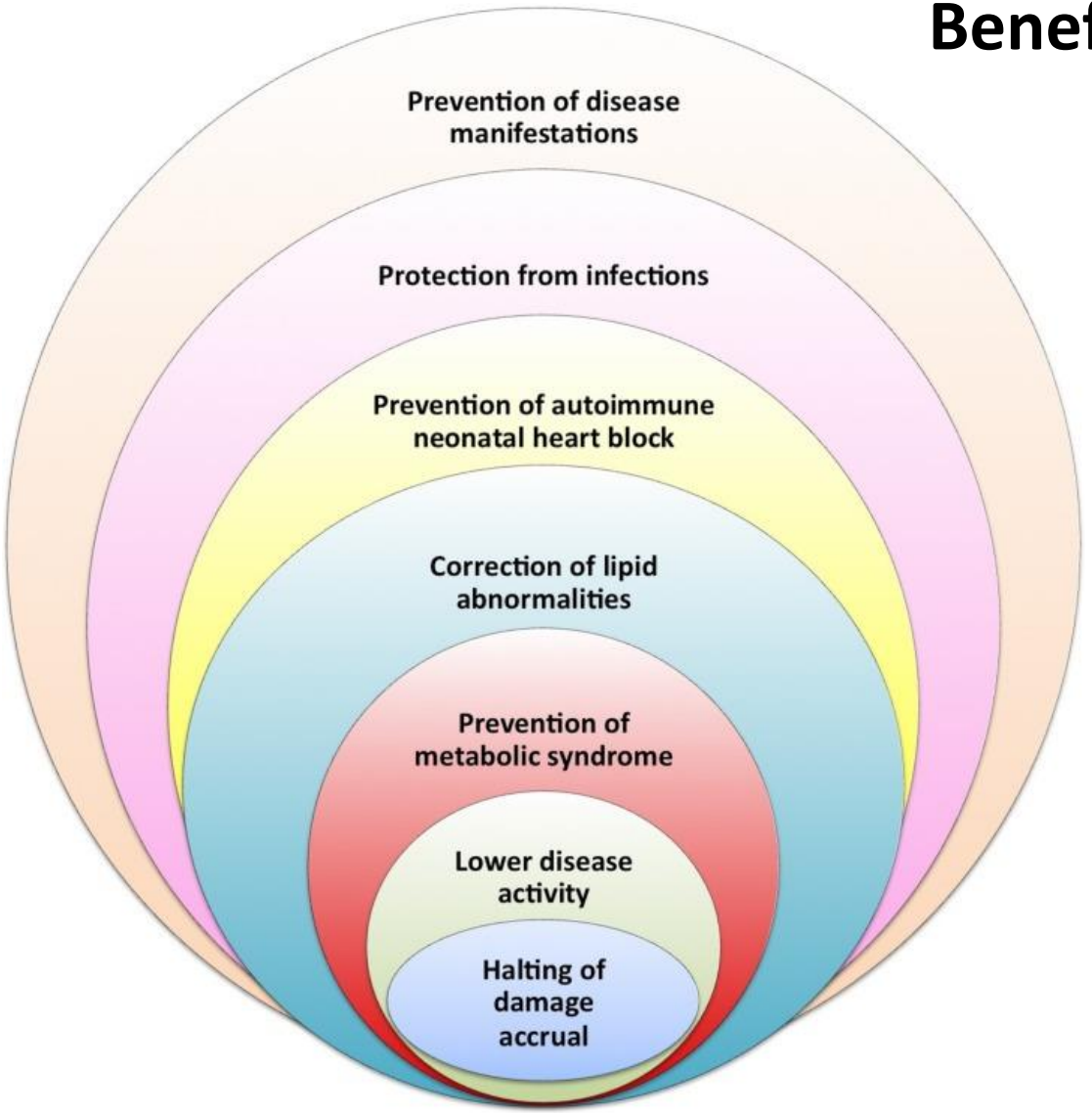
- Cs have dose dependent side effects
  - **Mother**: Metabolic, ocular,cardiovascular, bone, susceptibility to infection
- **Child: High dose:** Increase prematurity and low birth weight
- Most side effects related to genomic action of Cs – non-genomic action (at ≥ 100 mg) less side effects
  - Buttgereit Arthr Rheum 2004
  - Ruiz-Irastorza G J Autoimmun 2014&2016; Palmsten et al Pharmacoepidem Drug Safety 2018

Use of corticoids in pregnancy

- To avoid toxicity in mother and child – limit peroral prednisone dose 5-10 mg/day
- Mild to moderate flares: short term high dose prednisone with rapid tapering or i.m. triamcinolone injection once
- Severe flares: methylprednisolone pulse 250-500 mg for 3 days + immunosuppressive therapy, then peroral prednisone with tapering

Danowski A et al. J Rheumatol 2006; Thamer M et al. J Rheumatol 2009

Benefits of antimalarials in lupus pregnancies



Fanouriakis Lupus Sc Med 2019

AM reduce lupus activity, less prednisone use at continuation of HCQ throughout pregnancy; reduce preeclampsia and IUGR;
reduce risk for CHB.

Risk of flare during pregnancy increased in patients not taking HCQ: OR 3.6

AM in addition to standard therapy may reduce risk of adverse pregnancy outcomes in women with APS not responsive to ASA+heparin/LMWH

Clowse at al. A&R 2006; Koh et al. Lupus 2015; Skorpen et al Arthr Care Res 2016, Seo et al Lupus 2019

30 yr old patient with previous LN

- Biopsy proven WHO class 4 LN treated with corticoids and IV cyclophosphamide 3 years ago. Maintenance with mycophenolate mofetil 2g/day. HCQ 400mg/d, 5 mg prednisone/d.
  LN clinically and laboratory quiescent for the last 2 years.
  Patient wants a pregnancy
- Stop MMF, switch to azathioprine, wait for control of disease activity and continue with AZA, HCQ and Pred in a future pregnancy.

Fischer-Betz et al. Rheumatology 2013

Immunosuppressives in CTD/vasculitis pregnancy

Pregnancy compatible DMARDs	Comment
Azathioprine	TPMT testing before start of therapy; keep dose at 2 mg/kg/day during pregnancy
Chloroquine, hydroxychloroquine	Keep dose of chloroquine at 250mg/day or hydroxychloroquine 5 mg/kg/day
Ciclosporine, tacrolimus	Steroid-sparing, dose adjustment according to trough levels
Prednisone	Keep dose below 10 mg/day if possible. High dose at organ flares
DMARDs to be avoided	**Insufficient knowledge or teratogenic**
Rituximab, Belimumab	Consider only at severe maternal disease
Tofacitinib, Baricitinib	Tofacitinib: data insufficient; Baricitinib: no data- **avoid**
Mycophenolate derivates, Cyclophosphamide	Teratogens, discontinue before pregnancy

Flint et al. Rheumatology 2016; Skorpen et al. ARD 2016

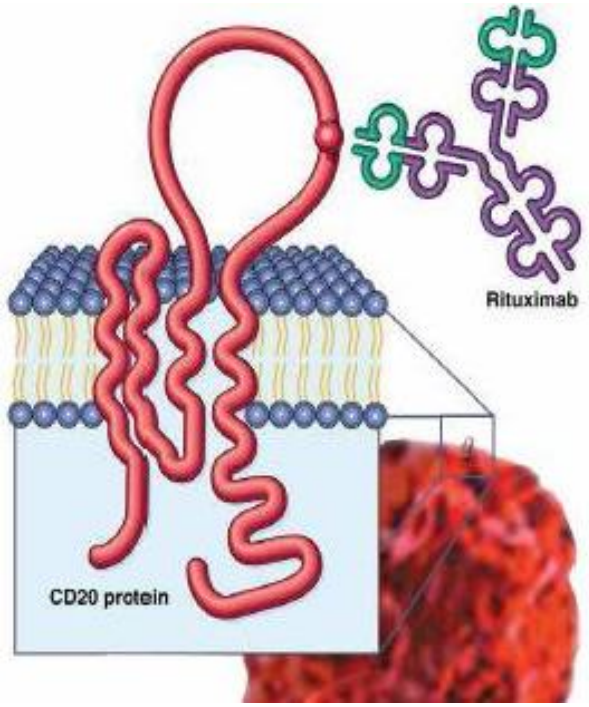
Patients refractory to standard therapy

- Patients with severe flare not-responsive to standard therapy – how to treat them?
- Options: **Cyclophosphamide** in 2nd/3rd trimester;
  Intravenous immunoglobulin;
  Biologics with limited pregnancy experience
- Unsolved question: use of teratogenic drugs in the 2nd and 3rd trimester?

Case: SLE with severe trhombocytopenia

- Pregnant SLE patient with previous malar rash, inflammatory arthritis, thrombocytopenia and leukopenia. Pre-conception platelet count stable at 90,000, therapy with HCQ + 5 mg pred. Uncomplicated pregnancy until routine follow up at week 29. Platelet count now: 30,000. Prednisone is increased to 20 mg daily but platelet count falls to 22,000 and she has noticed increased bruising on her legs and forearms.
  Discussion: increase prednisone or give Rituximab?

Rituximab (RTX) before/in pregnancy



256 pregnancies reported, no adverse effect on children at pre-conception or 1. trimester exposure

RTX prophylactic? 5 x maximal half-life is 110 days. A patient could try conception 3.5 mo after last infusion

The data from neuromyelitis optica and MS seem to support that relapse of serious disease may be prevented by preconceptional RTX

Chakravarty et al, Blood 2010

Belimumb (BEL) in pregnancy

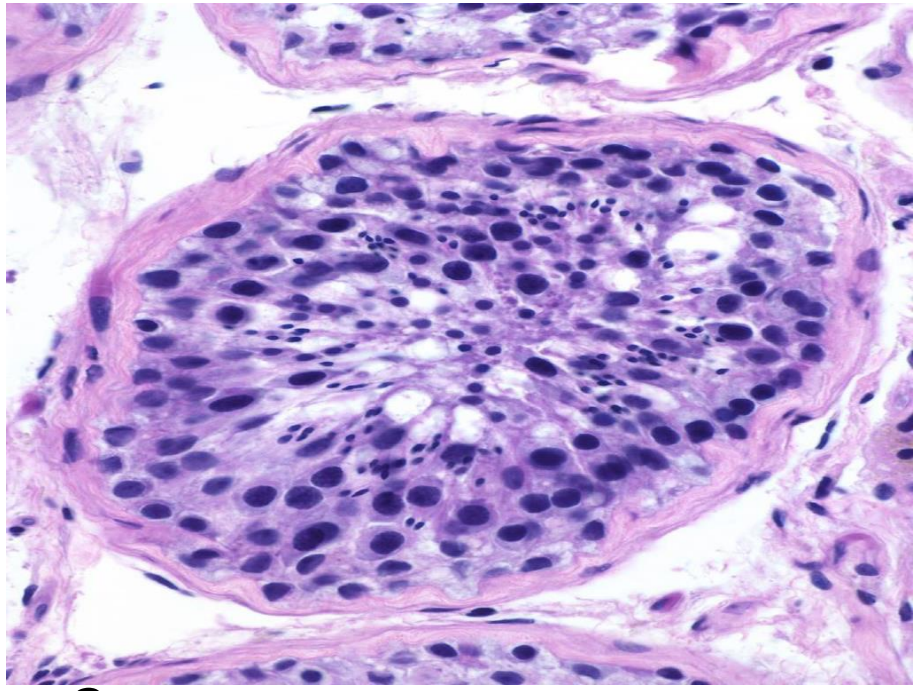
- BEL is steroid-sparing, has effect on musculoskeletal, mucocutaneous, hematologic and general constitutional features of SLE – could it be a choice in pregnant patients refractory to standard therapy?
- Animal studies and case reports are reassuring
- A prospective study on Belimumab in pregnancy is ongoing: Landy H et al. Obstet Gynecol. 2014 May;123 Suppl 1:62S

Treatment of severe disease in the 2. or 3. trimester with cyclophosphamide

Author	No of pregnancies	Diagnosis	Complication	Outcome
Durodola 1979 Lam 2006	1 1	Burkitt lymphoma Burkitt lymphoma	Malignant disease	Healthy term infant Healthy term infant
Nelson-Piercy 2016	2	ILD; Goodpasture synd.	respiratory compromise; Alveolar bleeding	Premature baby; Healthy term infant
Soh et al. 2009	1	Wegener`s granulo-matosis	Alveolar bleeding	Term, healthy infant
Parks et al. 2012	1	SLE – flare LN	Renal failure	Preeclampsia, preterm birth, healthy baby
Clowse et al. 2005	2	SLE – flare LN	Nephrotic syndrome; severe hypertension; renal insufficiency	Fetal death

Are antirheumatic drugs gonadotoxic in men?

- Do medications harm fertility?
  - Spermatogenesis



- Harmful for offspring?
  - Increase abortion?
  - Increase malformations?
  - Long-term adverse effects in children?

Micu M et al. Semin Arthritis Rheum. 2018

Drugs and spermatogenesis

Drug	Publications	Comment
Corticosteroids Arnaud et al Arthr Rheum 2017	Inverse relationship between prednisone dose and reduced bioactive testosterone	Other effects of corticosteroids on spermatogenesis not known
Azathioprine Dejaco C.Gastroenterol 2001	No quantitative or qualitative abnormalities of sperm observed in men with IBD	No impairment of male fertility
Methotrexate *Mouyis et al. SAR 2018*	Data from case reports/series not consistent, most no effect, some oligospermia	No indication for infertility caused by low dose weekly MTX
TNF inhibitors Infliximab,Adalimumab, Etanercept, Certolizumab	No quantitative or qualitative abnormalities of sperm in controlled studies (Villiger P 2010; Micu M 2013; Perrier S ARD 2013; Ramonda 2014; Heppt 2017; Valer 2017)	No impairment of male fertility, sperm quality often better with TNFi

Immunosuppressive drugs in fathers

Drug	No. of pregnancies reported	Outcome
Azathioprin, Cyclosporin (Cs), Tacrolimus: ca. 1000 AZA, 200 Cs, 100 TAC Data from transplant recipients and autoimmune disease. AZA, Cs and TAC often used in combination	> 1000	Compared to healthy or disease matched controls no increase in miscarriage or congenital malformations Preconceptional withdrawal not necessary
Mycophenolate mofetil Jones Progr Transpl 2013;Morken2015; Engeland Br J Clin Pharm 2012; Midtvedt Transpl 2017	Ca. 400	Compared to disease matched controls no increase in congenital malformations May be continued, but no consensus
Methotrexate	Ca. 1000	No increase in miscarriage or birth defects
TNF inhibitors Infliximab, Adalimumab, Etanercept Wallenius et al. A&R 2015,	547	Compared to healthy controls no increase in miscarriage or congenital malformations Preconceptional withdrawal not necessary

Conclusion: MTX in men

- Register-based studies including ca. 1000 pregnancies with fathers exposed to weekly low-dose MTX have not shown an increase in adverse pregnancy and child outcomes

- Rheumatologists should not stop a highly effective therapy in men with rheumatic disease – *Flint et al. 10th International Pregnancy Conference 2018 in Bern*

Conclusion

- Review all medications together with the patient before or early in pregnancy
  - Explain which drugs should be continued and why
  - Explain which drugs must be discontinued and when
- Individualize therapy according to disease activity at conception, during pregnancy and lactation
- Balance the necessity to control maternal disease activity and to prevent harm to the fetus or child

Østensen M. Curr Op Rheumatol 2014

Conclusion-2

- In women of reproductive age use drugs:
  - with the largest evidence of safety for the unborn, considering the possibility of an unplanned pregnancy
- In case of a severe flare in pregnancy:
  - drugs with insufficient pregnancy data or with developmental risks might be the only treatment options even during pregnancy.
- Counsel male patients in regard to drugs and reproduction