Managment of RA in pregnancy

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Problems of RA management before and during pregnancy

- The patient with a desire of children in need of therapy
- The patient with good response to therapy and a desire of children
- The patient who gets a flare during pregnancy
- Post partum flare

Case 1: 32 yr old woman with small joint arthritis

- **She developed swelling of her PIP joints 2-5 six weeks ago and experienced morning stiffness and pain. Diclofenac 50 mg x 3/day has relieved pain. She plans to have a pregnancy in the near future.**
- **Is this feasible at this stage of polyarthritis?**

Problem: Early stage of polyarthritis

- Diagnosis not established
- Progression of disease still unknown
- Disease modifying therapy not established

- Best solution:
  Postpone pregnancy
  Wait for development of disease
- Start effective therapy to get disease under control

Patient with early RA

- **The patient meets after 2 months for a second visit. New laboratory tests show positivity for rheumatoid factor and for anti-citrullinated protein antibodies (ACPA). Active arthritis is present in all PIP joints, in both wrists and in MTP joints 2-5 in both feet.**
- **Patient still wants a pregnancy.**

Questions:

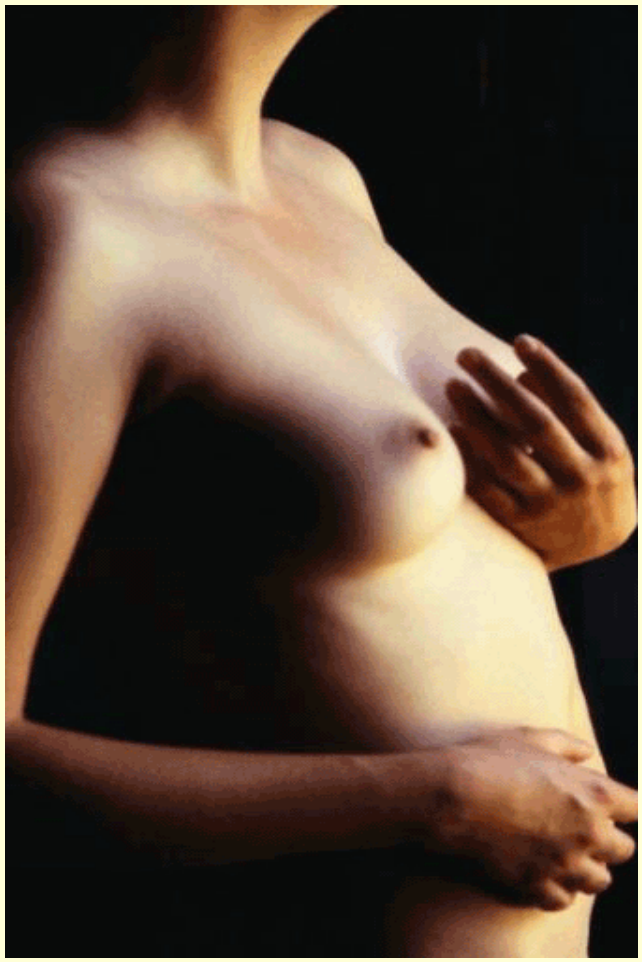
- Will the disease improve during pregnancy?
- Which drug therapy is compatible with pregnancy?
- Has the patient any risk factors for adverse outcome during pregnancy?

Course of RA during pregnancy

Improvement in 48-75%

Remission in 16-27%

25% remain active during pregnancy and need therapy



Predictors of activity during pregnancy

- The patient is positive for ACPA, less prone to improve during pregnancy
  - In a prospective study of 118 patients, 75% of patients negative for RF and CCP antibodies improved compared to only 39% of those positive for RF and CCP antibodies.

- The patient has still active disease
  - Increased risk for adverse pregnancy outcome

Outcome of pregnancy in RA – Dutch prospectiv Study de Man YA et al, Arthritis Rheum 2009

Outcome of 152 RA pregnancies compared to healthy pregnant women

- Activity of RA well controlled
  - Pregnancy outcome = healthy women
  - RA active during pregnancy
  - Reduced birth weight
  - Low-birth-weight (<2500g) not increased
- Use of Prednison: prematurity
- Rate of preeclampsia not increased

Which therapy is compatible with pregnancy?

- Monotherapy with MTX or other DMARD
- Combination therapy
  - MTX – SZ – Antimalarials
  - MTX – CyA - Prednisone
- A TNF inhibitor
- Abatacept, Tocilizumab
- Rituximab

Prescribing in the patient who plans a family

- Therapy should act fast and get the patient into remission
- Therapy should be safe in the first trimester
- MTX alone or in combination only during safe contraception
- Biologics with insufficient pregnancy experience should be avoided

Immunosuppressives with a good record during pregnancy

Arthritis Res Ther. 2006;8:209

Drug	**Pregnancy records**	**Precautions**
Sulphasalazine	> 2000	Folate supplementation
Antimalarials	> 500	Prefer HChl
Azathioprine	> 2000	Dose =2mg/kg/d
Cyclosporine	> 800	Control blood pressure

Prophylactic withdrawal before pregnancy

Drug	Documented risk	Withdrawal
Methotrexate	5 -10%	3 months before
Leflunomid	Only in animal studies Otis study: no human teratogen	Washout before recommended

Methotrexate (MTX) in pregnancy

Experience from case reports and series

- **At first trimester exposure :**
  - Risk of miscarriage
  - 5-10% risk of congenital malformations
  - MTX is teratogen, can cause multiple anomalies
  - **Conclusion: MTX must be discontinued 3 months before a planned pregnancy** Lewden et al. J Rheumatol 2004

Leflunomide in pregnancy – Otis study

Chambers C et al. Arthr Rheum 2010;62:1494

- Exposed and non-exposed RA pregnancies were prospectively studied
  - 63 pregnancies exposed during the 1. Trimester
    108 non-exposed RA pregnancies
- No difference in birth weight, no increase of congenital malformations in the leflunomide group
- Conclusion: Leflunomide not a strong teratogen

Risk factors for pregnancy outcome

- Other antibodies may be present in a RA patient:
- SS-A (anti-Ro) antibodies
  - Risk for development of neonatal lupus syndromes
- Phospholipid antibodies
  - Risk for miscarriage, intrauterine growth restriction, premature delivery

Case 1 continued. The patient with good response to therapy planning a pregnancy

- The patient‘s RF and ACPA-ab positive RA responds well to a combination of adalimumab and methotrexate and gets into remission.
  She now plans a pregnancy in the near future.

Therapeutic problems in this patient

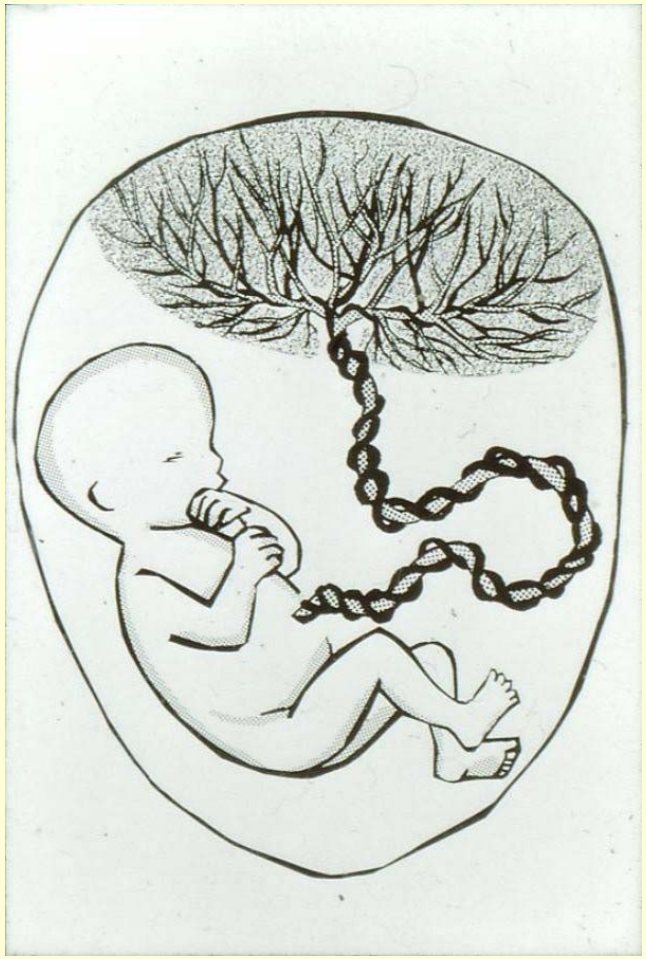
- The disease is well controlled with adalimumab + MTX
- Therapy has to be stopped because of a desire for children:
  - Unpredictable when the patient will conceive
  - A flare may occur
  - Pregnancy cannot be postponed because of the age of the patient

Biological agents in pregnancy

Biologicals that are monoclonal antibodies are of the IgG1 type

IgG1 crosses the placenta from gestational week 14

In late pregnancy maternal and fetal serum concentrations are similar



TNF inhibitors in pregnancy

A total of >750 pregnancies under therapy with TNF inhibitors have been reported

- > 400 Infliximab
- > 200 Etanercept

} mostly 1. trimester

- Adalimumab
- Certolizumab
- Ca. 170 treated throughout

Outcome after exposure to TNF inhibitors

- Pregnancy outcome: No increase in miscarriage, prematurity or major birth defects
- Congenital anomalies have been reported, but are not increased over normal population

If the patient had received Rituximab 6 wks before pregnancy – is there a risk?

- Outcome of 153 pregnancies exposed to Rituximab Chakravarty et al, Blood 2010

- 90 (59%) live birth
- 33 (22%) miscarriage
- 28 termination of pregnancy
- 2 birth defects, 5 neonatal infections
- Hematologic abnormalities in 11 neonates

When to stop biological agents?

Drug	Risk for congenital anomaly	**Stop before/at conception**
Infliximab	Data insufficient	At Conception
Adalimumab		At Conception
Etanercept		At Conception
Abatacept Tocilizumab		3 mo before planned pregnancy
Rituximab		6 mo before

The patient with a flare of arthritis during pregnancy

- The patient has become pregnant. MTX was discontinued before pregnancy. Adalimumab was stopped at week 7. After stop of therapy the disease relapses at week 11 and remains active during pregnancy.
- What treatment is possible during pregnancy?

Problems with DMARD during pregnancy

- Most classical DMARD have a delay in onset of effect
- At present no fast acting drugs (except for corticosteroids) are proven as safe during pregnancy
- Solution: keep patient on safe DMARD throughout pregnancy

Can TNF inhibitors be continued during pregnancy?

- Issue under debate

- In RA most exposures have been around conception or at 1st trimester
- At intentional use throughout pregnancy: No increase in adverse neonatal outcomes reported, but risk for increased susceptibility to infection BCGitis in child exposed in utero

Administration of TNF inhibitors in pregnancy Østensen&Forger, Curr Opinion Rheumatol 2011

- Depends on severity of disease – risk/benefit
- TNF inhibitors differ in structure: without Fc part no active transplacental transport
- Recommendation: Discontinue infliximab, etanercept, adalimumab, golimumab as soon as pregnancy is recognized.
- In severe cases discontinue at week 30
- Compatibility of certolizumab needs confirmation

Treatment of acute arthritis during pregnancy

- **Intraarticular corticosteroids**
- **Oral corticosteroids**
- **Non-steroidal antiinflammatory drugs until gestational week 32 or paracetamol (+/- Codein)**
- **Immunosuppressive drugs**

Corticosteroids in pregnancy

Park-Wyllie, Teratology;2000

- **Prednisone** >15 mg/d increases the risk of maternal and fetal side effects
- May increase the risk of oral clefts

- **Recommendation:**
  - **Prednisone maintenance therapy at or < 15 mg/day in the 1st trimester**
  - **only 5-10% unbound prednisolone present**

Risks of NSAID during pregnancy

- Constriction of the fetal ductus arteriosus
  - Development of pulmonary hypertension
- Impairment of fetal renal function
  - Oligohydramnios

  can occur at any stage of pregnancy, is dose dependent and reversible after discontinuation of maternal treatment

Discontinue NSAID at week 32 or continue under close ultrasonographic monitoring of the fetus

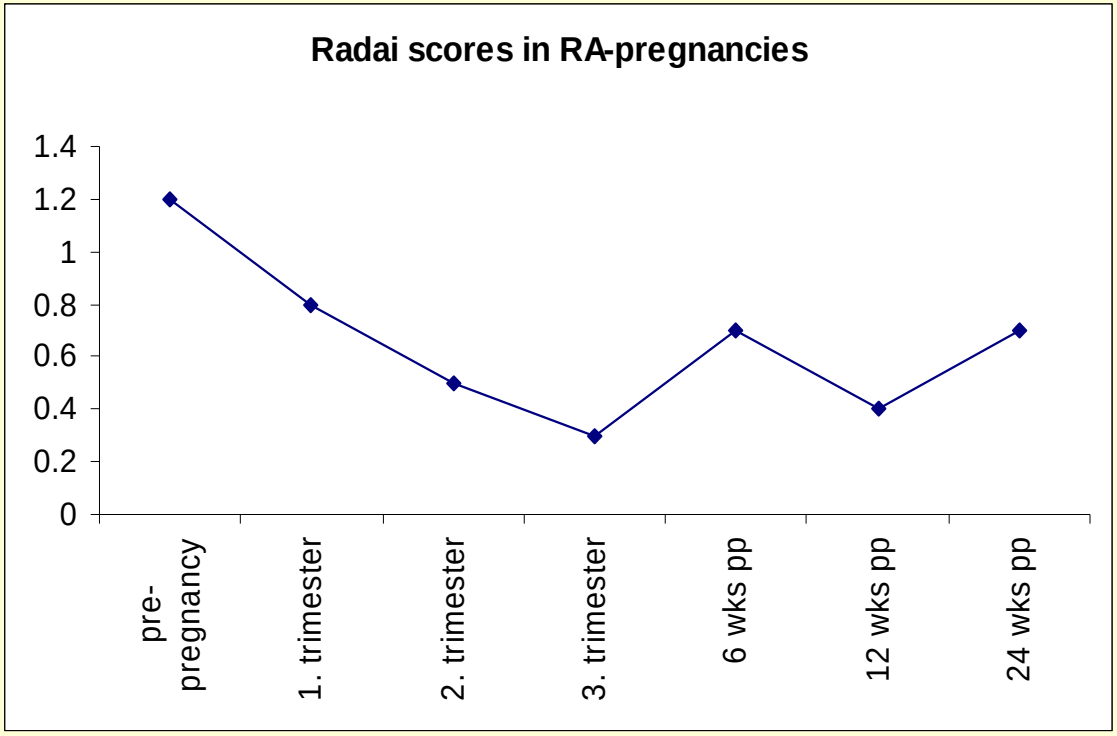
The actively ill RA patient may need combination therapy

Adapted to the stage of pregnancy:

- Corticosteroids
- Immunosuppressive drugs
- Local therapy of inflamed joints
- Analgesics and NSAID
- Physiotherapy, Ergotherapy

The post partum flare in RA

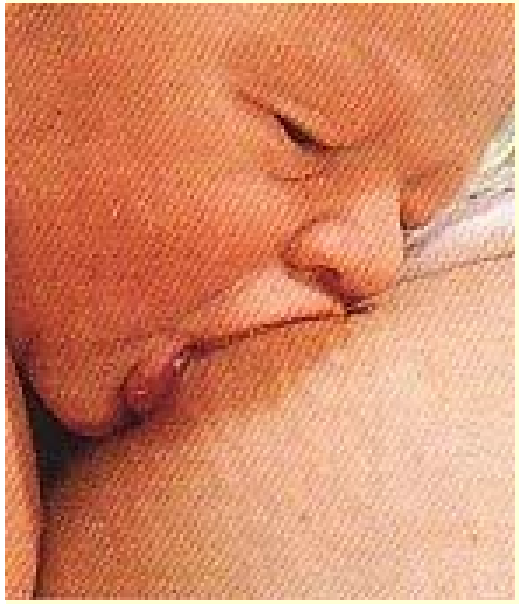
Nelson & Østensen 1997&2004, Barrett et al. 2001, de Man et al. 2008



Prevention of a post partum flare

- Ca. 90% of RA patients experience a post partum flare within the first 3 months after delivery
- Start effective therapy as soon as RA activity relapses or keep patient on compatible DMARD throughout pregnancy
- Corticosteroids, Sulfasalazine, Antimalarials, azathioprine, NSAID are compatible with nursing

Antirheumatic drugs during lactation Østensen &Motta, Nature Clin Practice Rheumatology 2007;3:400-406



Very few studies

Often passage into breast milk known but effect on nursing child not known.

In general, <10% of the therapeutic infant dose of the drug
Ingested from breast milk: no harm

TNFα inhibitors during lactation

Drug	Detected in milk	Effect on infant
Infliximab	No	No adverse effect reported
Etanercept	Yes	No adverse effect reported
Adalimumab	Yes	No adverse effect reported

Key messages

- Before pregnancy: assess risk factors for mother and child
- Adjust therapy to drugs compatible with pregnancy and lactation
- TNF inhibitors and rituximab appear not as strong human teratogens, but may increase susceptibility for infections in exposed children

Key messages

- Corticosteroids, Sulfasalazine, Antimalarials, Azathioprine and Cyclosporine are compatible with pregnancy
- A flare post partum should be treated immediately
- Corticosteroids, Sulfasalazine, Antimalarials, azathioprine, NSAID and some TNF inhibitors are compatible with nursing

END

Thank you!