How safe are anti-rheumatic drugs during pregnancy?
Monika Østensen and Frauke Förger

Rheumatic diseases may be active during pregnancy necessitating drug treatment in order to control maternal disease activity and ensure a successful pregnancy outcome. The present literature survey of the last 2 years does not profoundly change the recommendations given in recent reviews: the teratogenic drugs cyclophosphamide, methotrexate, mycophenolate mofetil, and biologics without or with few pregnancy data must be withdrawn before a planned pregnancy. Leflunomide has up to date not shown to be a human teratogen. Drugs that can be used throughout pregnancy include corticosteroids, sulfasalazine, antimalarials, cyclosporine, tacrolimus and azathioprine. Among biological drugs extended pregnancy experience exists only for TNF-inhibitors. The effect of immunosuppressive drugs and biologics on male reproductive function is only partly known.

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Introduction
Planning pregnancy in women with rheumatic diseases requires adjustment of therapy to drugs, which keep the underlying maternal disease quiescent and are compatible with embryonic and fetal development. Withdrawal of all drugs administered before conception resulting in a disease flare may be equally disastrous for pregnancy outcome as continuation of agents that are able to harm the developing child.

Information on usage of drugs during pregnancy is limited, since pregnant women are never included in drug trials and knowledge usually accumulates over the years from inadvertent drug exposure during unplanned pregnancies. Regular updates of information are therefore timely. This survey is based on a literature search on immunosuppressive, antirheumatic drugs used in pregnancy published during 2010–2012. Several excellent reviews have given a complete overview of published experience of antirheumatic drugs in pregnancy, and these should be consulted for details [1–3,2,3].

An overview of pharmacotherapy in rheumatic diseases
Risks of pregnancy in the mother with rheumatic disease depend on disease activity shortly before conception and throughout pregnancy, extent of organ involvement and presence of certain types of autoantibodies (Table 1). Risks for the fetus are related to maternal disease activity, presence of autoantibodies and maternal therapy (Table 1). As shown in Table 2, drug therapy of rheumatic diseases differs and will as a rule be tailored according to type of organ involvement, severity of the disease and individual response to treatment. Adjustment of therapy in a patient planning a pregnancy or consulting during early pregnancy will aim at optimal disease control in the mother and healthy development of the child (Figure 1).

Drugs to be discontinued before pregnancy
Methotrexate (MTX) and cyclophosphamide (CYC) inhibit cell division and are teratogenic in animals and humans. No new reports on CYC in autoimmune disease pregnancies have been located. A teratogen update has analyzed all the published cases with MTX exposures to doses between 7.5 mg/week for rheumatic diseases and up to 150 mg/week for induction of abortion for the proportion of all malformations [4**] and compared with the same proportion from the Metropolitan Atlanta Congenital Defects Program [5]. The data have confirmed that the sensitive period for the production of malformations is 6–8 weeks after conception for doses greater than 10 mg of MTX/week. Higher doses increase the risk for MTX embryopathy including cardiac defects, pulmonary atresia, craniosynostosis, and limb deficiencies [4**].

Two new studies have addressed pregnancy outcomes in men treated with MTX. A prospective study of men treated with weekly doses 7.5 mg and 30 mg of MTX three months before or until conception found no child with birth defects in 42 pregnancies [6]. A population based study of 50 pregnancies with fathers exposed to MTX has reported two children with orofacial malformations [7].

Mycophenolate (MMF) is used successfully in the treatment of lupus nephritis. First trimester exposure increases the risk for multiple congenital malformations with a special phenotype including microtia, auditory canal atresia, cleft lip and palate, micrognathia, hypertelorism, ocular coloboma, short fingers and hypoplastic
nails [8]. A new prospective study has investigated 57 pregnancies exposed to MMF in the first trimester [9]. 45% of the pregnancies ended in spontaneous abortion. Six out of 29 live born children showed congenital malformations, which in four infants had a clinical phenotype consistent with mycophenolate embryopathy [9]. The malformation rate for all the pregnancies after MMF exposure was 26%. Patients who start treatment must be informed that discontinuation of MMF is necessary at least 6 weeks before trying conception, and be advised to use effective birth control during therapy.

Leflunomide

Leflunomide, an inhibitor of pyrimidine synthesis was shown to be teratogenic in rats, rabbits and mice, and therefore labeled as contraindicated in human pregnancy [10]. A few case reports during the years 2000–2010 were not conclusive until the Organization of Teratology Information Specialists (OTIS) published the results of a prospective study of birth outcomes in women exposed before or during pregnancy to leflunomide [11**]. Comparing pregnancy outcomes of 64 patients with RA exposed during the first trimester to 108 RA pregnancies not exposed neither showed increase in birth defects nor any recognizable malformation pattern [11**]. This result was confirmed in additional 45 pregnancies of patients who were exposed to leflunomide either within two years before conception or during the first trimester [12]. These data indicate that leflunomide is not a strong human teratogen though due to the limited number of exposed pregnancies contraception is recommended during pregnancy.

<p>| Course of maternal disease during pregnancy and fetal risks in some rheumatic diseases |
|---------------------------------|---------------------------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Disease</th>
<th>Autoantibodies with risk for pregnancy</th>
<th>Active during pregnancy</th>
<th>Fetal risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis</td>
<td>Rare*</td>
<td>Improves in 50–75% of pregnancies, 10–25% remain active</td>
<td>Rare — limited to very active RA or to therapy</td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td>No</td>
<td>60% of patients remain active, 20% flare during pregnancy</td>
<td>No</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>Antiphospholipid antibodies, anti-SS-A, anti-SS-B</td>
<td>50% of patients have mild to moderate activity, severe flares occur in about 25% of pregnancies</td>
<td>Miscarriage, intrauterine growth restriction, prematurity, congenital heart block</td>
</tr>
<tr>
<td>Systemic sclerosis</td>
<td>Rare</td>
<td>No major effect of pregnancy on disease activity</td>
<td>Intrauterine growth restriction, prematurity</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>Rare</td>
<td>No major effect of pregnancy on disease activity</td>
<td>Miscarriage, intrauterine growth restriction, prematurity</td>
</tr>
</tbody>
</table>

* Antiphospholipid antibodies and anti-SS-S/B can occur in other rheumatic diseases as well, but much less frequent than in SLE.

Table 2

<p>| Drugs used in different rheumatic diseases in the non-pregnant and pregnant state |
|----------------------------------------|----------------------------------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Disease</th>
<th>Drugs used in the non-pregnant state</th>
<th>Drugs compatible throughout pregnancy</th>
<th>Indication for therapy in pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammatory rheumatic disease:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rheumatoid arthritis, juvenile idiopathic arthritis</td>
<td>Antimalarials, Salazopyrine, Methotrexate, Prednisone, Intraarticular corticosteroids, TNF inhibitors, Abatacept, tocilizumab, rituximab Nonsteroidal anti-inflammatory drugs (NSAID)</td>
<td>Antimalarials, Salazopyrine, Intraarticular corticosteroids NSAIDs until gestational week 32</td>
<td>Maintenance of remission, treatment of an arthritis flare</td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td>NSAIDs Salazopyrine, Intraarticular corticosteroids, TNF inhibitors</td>
<td>NSAIDs until gestational week 32 Salazopyrine, Intraarticular corticosteroids</td>
<td>Treatment of an arthritis flare (pain and stiffness are prominent in AS)</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>Antimalarials, Prednisone Azathioprine Cyclosporine, Tacrolimus Mycophenolate mofetil (MMF) Cyclophosphamide Rituximab Belimumab</td>
<td>Antimalarials, Prednisone Azathioprine Cyclosporine, Tacrolimus</td>
<td>Maintenance of remission, treatment of flare and severe organ manifestation</td>
</tr>
<tr>
<td>Other connective tissue diseases:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polymyositis, Dermatomyositis, Systemic vasculitis, Systemic sclerosis</td>
<td>Methotrexate cyclophosphamide, Prednisone, Azathioprine Intravenous immunoglobulin, Rituximab, ACE inhibitors, Endothelin receptor antagonists, Prostaglandin analogs Phosphodiesterase inhibitors</td>
<td>Prednisone, Azathioprine Intravenous immunoglobulin Prostaglandin analogs Phosphodiesterase inhibitors</td>
<td>Maintenance of remission, treatment of flare and severe organ manifestation</td>
</tr>
</tbody>
</table>
use and a washout procedure in case of a planned or unintended pregnancy.

Drugs that can be used throughout pregnancy

Corticosteroids
A controversy exists as to an association of first trimester exposure to corticosteroids and a significant increase of oral clefts [13]. A new population based study with 51,973 corticosteroid exposed pregnancies did not find an increase of orofacial clefts regardless of type of corticosteroid administered (oral, inhalation, nasal spray, topical) [14**]. After completion of placenta development, all corticosteroids are partly inactivated by 11-beta-hydroxylases of the placenta with relative protection of the fetus. Prolonged use of corticosteroids increases the risk of preterm delivery, intrauterine growth restriction, and the frequency of maternal side effects like hypertension, diabetes mellitus and osteoporosis. However, severe flares of rheumatic disease during pregnancy most often need doses of corticosteroids exceeding 20 mg/day for rapid control of symptoms.

Hydroxychloroquine (HCQ) exerts a number of positive effects that are particularly beneficial for SLE patients [15]. These include prevention of lupus flares, lowering of lipid levels, and moderate protections against thrombosis [16], and reduction of development of congenital heart block (CHB) in children of mothers positive for anti-Ro/anti-La antibodies [17]. Even in anti-Ro/anti-La positive mothers with a previous child with CHB the recurrence rate of cardiac-NL was 64.6% lower in pregnancies exposed to HCQ compared with those unexposed [18]. The new data indicate that HCQ should be continued in SLE patients and other patients positive for anti-Ro/anti-La antibodies throughout pregnancy.

Sulfasalazine
A registry based Norwegian study has identified 589 pregnancies with exposure to antirheumatic drugs during the first trimester, thereof 74 exposed to sulfasalazine. No increase in congenital malformations was found in exposed children [7], confirming previous studies.

Calcineurin inhibitors
Cyclosporine (Cs) and tacrolimus are calcineurin inhibitors and inhibit the activation of T and B cells. Two forms of cyclosporine with different bioavailabilities are available: CsA and modified Cs (Neoral) the latter with much improved bioavailability. Most pregnancy experience is present for CsA and stems from registries of pregnant transplant recipients whereas experience from pregnant patients with autoimmune disease is limited to case reports and case series. Thus far, most of the studies of pregnancies exposed to CsA or Neoral have found an increase in premature delivery and low birth weight, but no increase of congenital malformations nor any particular malformation pattern [19,20]. Whether prematurity and low birth weight actually are a side effect of Cs or related to the underlying disease and comorbidities or multidrug therapy is not clarified. Pregnancy experience for tacrolimus is nearly exclusively related to transplant recipients, but a few case reports on patients with autoimmune diseases exist [20,21]. As with Cs no increase in the malformation rate or a malformation pattern has emerged. In patients with autoimmune disease refractory to other immunosuppressive treatment Cs or tacrolimus may be administered during pregnancy.
Azathioprine

In a systematic review and meta-analysis the effect of thiopurines (6-mercaptopurine and azathioprin) on birth outcome from female and male inflammatory bowel disease (IBD) patients were analyzed [22**]. The pooled analysis of five studies showed no significant association between thiopurines and congenital defects (OR 1.45; 95% CI 0.99, 2.13) or low birth weight (OR 1.01; 95% CI 0.96, 1.06). However, the analysis disclosed a significant increase for the association between preterm birth and women taking thiopurines (OR 2.28; 95% CI 0.67, 7.73), yet it remains unclear whether this was secondary to the drug or to active IBD [22**]. The findings confirm results in transplant recipients treated with AZA and support its use during pregnancy when indicated.

The pooled analysis of three studies showed no significant risk for congenital anomalies after paternal exposure at the time of conception to thiopurines [22**]. Another study evaluated the outcome of 46 pregnancies when fathers were exposed to thiopurines [23]. No significant difference in regard to unsuccessful pregnancies or congenital malformations was found compared with pregnancies fathered by patients who had never been treated with thiopurines or who stopped thiopurines more than 3 months before conception.

Biological drugs

TNF inhibitors: monoclonal antibodies infliximab, adalimumab and golimumab

The publications between 2010 and 2012 have by and large confirmed previous data on the use of infliximab, and adalimumab in pregnancy showing no increased risk of congenital malformations [24]. There are at present no human data for golimumab. TNF inhibitors that are complete antibodies containing an Fc part of IgG1 are actively transported through the placenta and reach high blood levels in the newborn after exposure in the late second and in the third trimester. Since the half-life of immunoglobulins is up to several months in newborn children, an increased risk for infection exists. BCG vaccination with a live attenuated form of Mycobacterium bovis given at 3 months of age resulted in fatal disseminated Bacillus Calmette-Guerin (BCG) infection in a 4.5 months old infant born to a mother with Crohn’s disease who received Infliximab throughout pregnancy [25].

Certolizumab (CZP), the pegylated Fab’ version of TNF antibody contains no Fc-part of IgG and shows minimal transplacental passage resulting in a median ratio cord blood to maternal levels of 3.9% whereas the median ratio of infliximab was 160% [27]. A recent study has published data from the global CZP safety database of 139 pregnancies with known outcome [28]. The proportion of live births, spontaneous miscarriages, and elective terminations for women directly exposed to CZP before or during pregnancy were comparable to those expected for the general US population of pregnant women. No increase in congenital malformations was observed [28]. In order to avoid an impaired immune response and risk for infection in the neonate and infant, TNF inhibitors should be discontinued as soon as pregnancy is recognized or, if warranted by the maternal disease, at least the TNF inhibitors with an Fc part should be discontinued before gestational week 30.

Male reproduction and therapy with TNFα inhibitors

The effect of infliximab, etanercept or adalimumab on spermatogenesis has been studied in 26 patients with spondylarthritis [29]. Sperm abnormalities were found both in patients without anti-TNF therapy and in 102 healthy controls. Patients on anti-TNF therapy showed significantly better sperm motility and vitality than untreated patients. Paternal exposure to anti-TNF at the time of conception in 46 pregnancies found one child with a septum defect and genital malformations [7]. Oligoasthenozoospermia and infertility was found in a patient treated with adalimumab [30]. Six months after stopping the TNF-inhibitor, sperm concentration increased to almost normal levels and morphology recovered completely. Taken together no major adverse effects of TNF inhibitors on male reproduction and offspring have been discerned [31].

Other biological agents

Exposure to rituximab, a B cell depleting monoclonal antibody, was analyzed in the global drug safety database including mothers with lymphoma, autoimmune cytopenias, and other autoimmune diseases [32]. Most of the cases were confounded by concomitant use of potentially teratogenic medications and severe underlying disease. Of 153 pregnancies with known outcomes, 90 resulted in live births. Twenty-two infants were born prematurely; with one neonatal death at 6 weeks. Eleven neonates had hematological abnormalities; none with corresponding infections. Four neonatal infections were reported (fever, bronchiolitis, CMV hepatitis, and chorioamnionitis). Two congenital malformations were identified: clubfoot in one twin, and cardiac malformation in a singleton birth [32]. Additional case reports confirm the results from the database [33].

Exposure to rituximab before conception or in the first trimester does not increase adverse events in the neonate.
whereas second and third trimester exposure leads to transient B cell depletion in the child. Although the rate of congenital malformations and neonatal infections have not been found increased, rituximab should be discontinued before pregnancy.

No publications on use of abatacept, tocilizumab and belimumab in human pregnancy have been located, therefore these agents must be discontinued 3 months before a planned pregnancy.

**Conclusion**

The survey confirms by and large the results on the safety of antirheumatic drugs during pregnancy that emerged in previous studies [1*,2,3]. New data have confirmed that leflunomide is not a human teratogen though washout procedures before conception or during an unplanned pregnancy are still recommended. The leflunomide data underscore the importance of prospective studies following the OTIS design: comparison of pregnancy outcomes in patients exposed versus patients not-exposed and compared to healthy pregnant women. Investigations into gonadotoxicity of several immunosuppressive drugs in males have documented no increased risk in offspring fathered by men treated with MTX, AZA or anti-TNF agents. However, more studies are needed to support absence of gonadotoxicity of MTX in men. At present, experience with biological drugs is limited which explains why most of them should be avoided during pregnancy less serious maternal disease requires treatment.

**Disclosure**

Monika Östensen has received speaker fees from Mepha; MSD; Pfizer; Roche; and UCB, Inc. Frauke Förger has received speaker fees from Roche and UCB.

**References and recommended reading**

Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
- of outstanding interest


   This review gives a detailed presentation of presentation of effects on female and male reproduction, presenting both animal and human data in regard to fertility, pregnancy and lactation.


   Presentation of both animal and human data on administration of MTX in pregnancy showing an increase in abortion and birth defects. Risk factors for the teratogenicity of MTX in humans are analysed.


   Prospective, controlled study of outcome of RA pregnancies exposed versus not-exposed to leflunomide and compared to healthy pregnant women showing no significant difference in outcomes between groups.


   A nationwide cohort study including 51 973 live births did not show an increased risk for orofacial clefts in pregnancies exposed to corticosteroids.


Cord serum and maternal serum levels of infliximab, adalimumab, and certolizumab were measured in 31 women with Crohn’s disease. Certolizumab was shown to have the lowest level of placental transfer.


