Connective tissue diseases and pregnancy

P. Saar, W. Hermann and U. Müller-Ladner

Connective tissue diseases (CTD) such as systemic lupus erythematosus diffuse or limited systemic sclerosis and numerous others affect women frequently during the childbearing period. Every pregnancy in a patient with CTD should be regarded as high-risk pregnancy, and requires intensive monitoring and immediate treatment of clinical problems. For these reasons, for women suffering from CTD, who are pregnant or who intend to become pregnant, an interdisciplinary setting addressing all aspects of rheumatology, ob–gyn and neonatology needs to be provided. This setting includes particular diagnostic tools and laboratory parameters prior to and during pregnancy as well as in the post-partal period. Aside overt organ dysfunction, key problems in pregnant CTD patients consist mainly of haemostaseological problems such as antiphospholipid antibodies, neonatal lupus erythematosus, congenital heart block and drug therapy of the underlying disease, which will be outlined in this review.

Introduction

As the patients suffering from connective tissue diseases (CTD) are predominantly young women between the ages of 20 and 40, two questions need to be answered firstly by the rheumatologist or gynaecologist: can I become pregnant? and, am I going to have a healthy baby? To both questions, in principle, the answer is ‘yes’. The basis for this positive response is, on one hand, the fact that fertility of patients with CTD appears not to be reduced. On the other hand, recent data of a prospective study revealed a rate of 66% live birth in systemic lupus erythematosus (SLE), and in 2005, two groups showed an even higher rates of 75% [1] and 85% [2]. To facilitate this high rate of healthy offspring, specific prophylactic and therapeutic actions need to be taken in each stage of pregnancy. However, as the risk for miscarriage, premature delivery and retardation of fetal growth is generally increased in CTD, the pre-conceptional diagnostics and treatment and their monitoring are of utmost importance, especially if an earlier pregnancy was associated with a neonatal or paediatric cardiological problem.

Diagnostic tools and laboratory parameters prior to and during pregnancy

Apart from the pre-maternity medical care performed by gynaecologist and physical examination by rheumatologist, the following laboratory parameters should be measured prior to pregnancy: (i) laboratory parameters: antinuclear antibodies with differentiation, especially SSA/SSB (Ro/La) antibodies, dsDNA-antibodies, C3-, C4-complement, antiphospholipid antibodies (anticardiolipin-IgG,-IgA,-IgM; phosphatidylserine-IgG,-IgM; β2-glycoprotein-I-IgG,-IgA,-IgM), lupus anticoagulant, creatinine, creatinine clearance and 24h-proteinuria, (ii) technical parameters: ECG, pulmonary function test with CO-diffusion capacity and echocardiography. In case of a likely risk for a congenital heart-block [SSA/SSB-antibodies positive, earlier pregnancies with congenital heart block (CHB)], a fetal echocardiography should be performed every 1–2 weeks between the 16th–28th week of pregnancy. To ensure a successful pregnancy and delivery, the following problems need to be addressed:

Effect of pregnancy on connective tissue disease and vice versa. As a recent publication [2] delineates that moderate to severe (high) lupus activity results in poorer outcomes of pregnancy including fetal loss and pre-term birth, monitoring of organ involvement, especially of chronic lupus nephritis, is mandatory. On the other hand, another group [3] could show that during pregnancy in patients with SLE and renal disease, changes in renal function are similar to those occurring in non-pregnant patients with lupus nephritis. However, monitoring of CTD activity needs to be performed during the complete pregnancy, as moderate to severe disease activity is present in at least 21% of the patients [2]. This increased disease activity was found to be evenly distributed between the three trimesters. Even more important, 58% of women with active lupus prior to pregnancy experienced a higher activity during pregnancy and lost their fetus in 42%. In contrast, of the patients with quiescent lupus prior to pregnancy, only 8% developed active lupus and only 11% lost their fetus. With regard to the patient herself, the maternal mortality rate in this study was only 1.1% (3/267) [2]. Another publication showed that flares of the disease occurred in 68% of the pregnant patients, but most of them were mild to moderate [4]. Table 1 summarizes the fetal risk factors during pregnancy.

Treatment options of the underlying CTD—the do’s and don’ts

To achieve a high rate of live and healthy offspring, the optimal anti-inflammatory and immunosuppressive therapy is also a key problem that needs to be addressed prior to pregnancy [5]. Conventional non-steroidal anti-inflammatory drugs (NSAIDs) and cyclo-oxygenase-2 (COX-2) inhibitors are possible to use against pain and arthritis but they need to be discontinued 6–8 weeks prior to delivery to avoid pre-term occlusion of the ductus arteriosus, and based on the present knowledge, COX-2 inhibitors should not be given during lactation. Prednisolone can be given during pregnancy as they are metabolized in the placenta. However, high doses (1–2 mg/kg) should be avoided in the first trimester and during lactation. With regard to disease modifying anti-rheumatic drugs (DMARDs), sulphasalazine and antimalarials have the safest record [6] and in case of active disease, they should not be withdrawn prior to or during pregnancy. In addition, it appears not to be necessary to advise against breastfeeding. Interestingly, recent data show that treatment of active CTD with azathioprine can be continued during pregnancy [6], especially because azathioprine is not converted into its active metabolite in the fetal liver. However,
it should not be given during lactation [5]. As few data exist for ciclosporin and there are alternatives with less side effects, it should be avoided or withdrawn whenever possible. Cyclophosphamide, mycophenolate mofetil, methotrexate and leflunomide are contraindicated during pregnancy and lactation because of their teratogenicity, mutagenicity and embroyotoxicity. Notably, leflunomide must be washed out prior to and in case of an unplanned pregnancy because of its long half-life, otherwise it can take up to 2 yrs until serum concentrations are reduced to a non-toxic level. On tumour necrosis factor-α (TNF-α) inhibitors, only limited data are available. However, case reports from ~100 patients indicate that at present there is no evidence linking TNF-α antagonists with embroyotoxicity, teratogenicity or increased pregnancy loss [7].

**Specific problems**

CTD-specific problems in pregnancy are ‘CHB’ and antiphospholipid antibodies. Neonatal lupus is triggered by maternal autoantibodies which pass the placental barrier, and specifically, anti-SSA/Ro52 and 60 kD antibodies are responsible for the development of CHB in up to 3% of the patients [8]. Recent data revealed also another potential risk for CHB when serotoninergic 5-HT[4] receptor autoantibodies are present [9]. As the fetal prognosis for CHB is poor, Doppler echocardiography is strongly recommended every 1–2 weeks in the vulnerable phase during the 16th–28th week of pregnancy, especially as the ECG in children of anti-SSA-positive and anti-SSA-negative mothers are not significantly different [10]. If there is a high risk for developing a CHB (earlier pregnancies with CHB, miscarriage, pathological fetal echocardiography), a (preventive) treatment with dexamethasone, azathioprine and/or even plasmapheresis can be applied [11]. If the fetal heart rate decreases <55 bpm, additional beta stimulation appears to improve the outcome [12]. Antiphospholipid antibodies, on the other hand, are associated with thrombotic events and miscarriage throughout the pregnancy. Relevant for clinical practice are the lupus anticoagulant, antiphospholipid antibodies, β2-glycoprotein antibodies, prothrombin antibodies and annexin V antibodies. Although each of the individual antiphospholipid antibodies can trigger thrombosis, the highest risk in patients with SLE appears to be associated with IgG antiprothrombin antibodies [13]. Another group underlined the importance of β2-glycoprotein antibodies [14]. Notably, pathological haemostaseological tests should be repeated during pregnancy as >50% of the antiphospholipid antibodies are only temporarily present. Although no generally accepted guidelines for treatment of women with positive antiphospholipid (APL) exist, current recommendations include 100 mg acetylsalicylic acid (ASS)/day until the 34th week for low to moderate APL titers. Notably, ASS 100 mg also enhances significantly the rate of conception in APL-positive women. During pregnancy, the combination of low-molecular heparin with aspirin to reduce pregnancy loss is recommended and generally used all over the world. However, when analysed in a Cochrane approach [15], unfractionated heparin in combination with ASS was regarded superior. In general, anticoagulation with coumarins is contraindicated, and only in individual cases, warfarin (14th–34th week) or intravenous immunoglobulin may be required.

In systemic sclerosis, predominantly in patients with the limited form, pulmonary arterial hypertension (PAH) is not unusual. However, few published data exist regarding PAH and pregnancy, especially in CTD. A recent study indicates that in a multidisciplinary approach and a targeted pulmonary vascular therapy, e.g. with nebulized iloprost, the outcome can be considerably

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**Table 1. Fetal risk factors, and risk factors for complications in SLE**

<table>
<thead>
<tr>
<th>Fetal risk factors</th>
<th>Risk factors for complications in SLE</th>
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<tbody>
<tr>
<td>Spontaneous abortion, miscarriage</td>
<td>every antiphospholipid-antibody</td>
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<tr>
<td></td>
<td>as well as lupus anticoagulant</td>
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<tr>
<td></td>
<td>low C3 complement</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>β2-glycoprotein-antibodies</td>
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<tr>
<td></td>
<td>low C3 or C4 complement</td>
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<tr>
<td></td>
<td>lupus nephritis</td>
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<tr>
<td></td>
<td>periconceptional hypertension</td>
</tr>
<tr>
<td>Prematurity</td>
<td>every antiphospholipid antibody</td>
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<tr>
<td></td>
<td>arterial hypertension during pregnancy</td>
</tr>
<tr>
<td></td>
<td>corticosteroids during pregnancy</td>
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<tr>
<td></td>
<td>(prednisone)</td>
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<tr>
<td>Intrauterine growth restriction</td>
<td>low C4 complement</td>
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<tr>
<td></td>
<td>age at pregnancy &gt;35 yrs</td>
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<tr>
<td></td>
<td>arterial hypertension during pregnancy</td>
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<tr>
<td>Flare of CTD during pregnancy</td>
<td>More than three flares before pregnancy</td>
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<td></td>
<td>flares with high activity</td>
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<td></td>
<td>termination of chloroquine 3 months</td>
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<td>prior to pregnancy, and because of</td>
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**Key messages**

- Every pregnancy in a CTD patient is a high-risk pregnancy.
- A pregnancy should be supported whenever possible, especially if there are no obvious medical circumstances that could impinge on pregnancy.
- Appropriate pre-conceptional diagnostic procedures are mandatory, especially if problems in earlier pregnancies have occurred.
- Specific major risk factors for an unfavourable outcome such as APL or nephritic syndrome, and contraindications such as severe organ dysfunction, such as cardiopulmonary or renal insufficiency, or pulmonary hypertension should be determined prior to conception whenever possible.
- After conception, gynaecological and rheumatological visits should be scheduled every 4 weeks until delivery, and at least one visit 4 weeks thereafter.
- Women with active lupus prior to pregnancy more frequently experience a flare of the lupus during pregnancy.
- There is a clear impact of lupus nephritis on outcome of pregnancy but not vice versa.
- If there is a risk for CHB, fetal echocardiography should be performed every 1–2 weeks between the 16th–28th week of pregnancy.
- Pathological haemostaseological tests (e.g. APL-antibodies) should be repeated during pregnancy as they can be only temporary.
- In patients with positive APL-antibodies, the combination of heparin with aspirin appears to reduce pregnancy loss significantly.
- Among the DMARDs, sulphasalazine and antiinflammatories have the safest record, azathioprine can be given if required to control the underlying disease.
- At present, from the few patients reported, there is no evidence that TNF-α antagonists are linked to embroyotoxicity, teratogenicity or increased pregnancy loss.
improved [16]. However, it needs to be noted that manifest pulmonary hypertension is one of the main contraindications for pregnancy in CTD patients.

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References