

## A. PREGNANCY

Pregnancy in patients with Sjögren's syndrome generally follows a normal course. Pregnancy outcomes are not different in patients with Sjögren's syndrome compared to controls.<sup>10</sup> While some women feel better during pregnancy, others may feel worse and sometimes it makes no difference. The same pattern may be repeated in a subsequent pregnancy, but this is by no means always the case.

There are a number of issues to be considered in relation to pregnancy and Sjögren's syndrome. The first concerns the question as to whether bringing up a child may not be too taxing for the patient. This is a personal decision which needs careful consideration.

The following topics will be discussed in this chapter:

1. the chance that a child will have an autoimmune disease including Sjögren's syndrome during her/his life-time
2. the risk for the child if the mother has auto-antibodies to SSA/Ro or antiphospholipid antibodies
3. the risk for the child if the mother takes drugs during pregnancy and lactation
4. thyroid gland disease and pregnancy

### 1. The child's risk for an autoimmune disease

#### ***Diseases in first-degree relatives of patients with primary Sjögren's syndrome***

Anaya *et al* examined the occurrence of auto immune diseases among first-degree relatives (parents, brothers, sisters, or children) of 101 female patients with primary Sjögren's syndrome (pSS) and of 124 matched controls without autoimmune disease.<sup>3</sup> The

The 3.85% prevalence of autoimmune diseases among first-degree relatives of control individuals is similar to the reported prevalence of such disorders in the general population<sup>5</sup> and in first-degree relatives of controls in other studies of familial autoimmunity.<sup>6,7</sup>

mean age at onset was 45 years, the mean duration of the disease 6 years and the mean age of both groups 54 years. One or more autoimmune diseases were found in 6.40% of patients' relatives as compared with 3.85% of controls' relatives (table 13.1). The most frequent auto immune diseases registered among the pSS patients' relatives were autoimmune hypothyroidism, systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). Five patients' relatives had more than one autoimmune disease (three had 2, one had 3, and one had 4 autoimmune diseases). These results are in line with a previous smaller study.<sup>4</sup>

A sex-specific-relative type occurrence of autoimmune diseases in the pSS families was observed when compared with control families. Nine of 101 pSS patients had a mother affected by at least one autoimmune disease compared with only one father affected. In the control group, there were 6 mothers and 2 fathers affected with one autoimmune disease.

**Table 13.1 Total number of autoimmune diseases in first-degree relatives of patients with pSS and of controls<sup>3</sup>**

<i>autoimmune disease</i> *	<i>first-degree relatives of</i>	
	<i>patients</i> (n=876)	<i>controls</i> (n=857)
pSS	4	0
SLE	8	1
RA	15	10
systemic sclerosis	2	0
PBC	1	0
vitiligo	4	3
MS	1	0
DM type I	3	1
hyperthyroidism	1	1
hypothyroidism	25	17

\* pSS: primary Sjögren's syndrome; SLE: systemic lupus erythematosus; RA: rheumatoid arthritis; PBC: primary biliary cirrhosis; MS: multiple sclerosis; DM: diabetes mellitus

## Conclusion

It can be concluded that the risk of a child of a mother with pSS to be diagnosed with an autoimmune disease at a mean age of 54 years is 6.4% (this is 1.66x higher than normal). If an autoimmune disease occurs, the chance that it is autoimmune hypothyroidism is 39%, RA 23%, SLE 12.5% and pSS and vitiligo 2% each. The risk will mainly apply to daughters and rarely to sons.

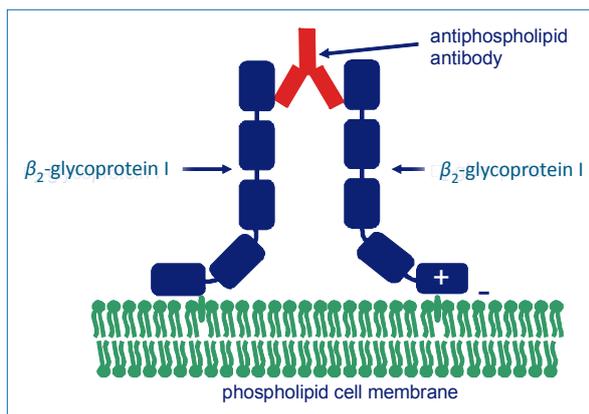
## 2. Pathogenic autoantibodies

### Antiphospholipid antibodies

Antiphospholipid antibodies are not uncommon in patients with Sjögren's syndrome. These antibodies are sometimes referred to by other names, depending on the method of testing used. They include for example the lupus anticoagulant and anticardiolipin antibodies. In general, they can be the cause of thrombosis (in both veins and arteries, an important difference from other causes of an increased risk of thrombosis), a low platelet count and miscarriages, often - but not always - between 3 and 6 months (figure 13.1).

If one of these problems has occurred and antibodies have been confirmed, the condition is called antiphospholipid syndrome. Treatment consists of anticoagulation. Tablets such as acenocoumarol sometimes in combination with low dose aspirin ("children's aspirin") are used for this anticoagulation treatment. Aspirin alone is insufficient to combat thrombosis.

With antiphospholipid syndrome, anticoagulation is also needed during pregnancy because this increases the chance of a successful pregnancy. Acenocoumarol is contra-indicated during pregnancy but low molecular



**Figure 13.1** The antiphospholipid antibodies interact with two  $\beta_2$ -glycoprotein I molecules. Via mechanisms that are not clarified to date, this binding leads to activation of endothelial cells and platelets and thrombosis.

weight heparin can be given, in combination with low dose aspirin (e.g. 100 mg/day) if required. Moreover, anticoagulation tablets and standard heparin are not effective for the protection of the pregnancy because they do not cross the placenta.

There is no consensus on how long patients with thrombosis due to the antiphospholipid syndrome should be treated with anticoagulants. Life-time anticoagulation may be necessary to decrease the risk on life-threatening thromboembolism.

### Antibodies to SSA/Ro

Children of women with antibodies to SSA/Ro in their blood run the risk of neonatal lupus (NL) either before or after the birth. These antibodies are mainly found in Sjögren's syndrome, subacute cutaneous lupus erythematosus (SCLE), systemic lupus erythematosus (SLE) and rheumatoid arthritis. SCLE is a relatively benign form of lupus erythematosus occurring in the skin. These antibodies can also be seen in a small percentage of healthy women. Children then also have a risk of developing NL during the pregnancy and after the birth. Conversely, NL only occurs if the mother, and therefore also the child, have antibodies to SSA/Ro.

### Clinical features of neonatal lupus

A circular rash on the face is sometimes the only abnormality, but the rash can also occur over the entire body (see figure 13.2). Skin abnormalities usually appear in the first two months of life and particularly following exposure to sunlight. Treatment is not necessary because the rash disappears without scars once the mother's antibodies have disappeared from the child (between 4 and 6 months). The only advice is to avoid exposure to sunlight during this period.

A congenital heart block occurs in 15-30% of the children with NL. More than half of these ultimately need a pacemaker. Other possible clinical features are listed in table 13.2.

Women with antibodies to SSA/Ro have about a 2-10% risk of their child developing NL, of which 20% with a congenital heart block. After one child with NL, subsequent children run a higher risk of developing NL (about 25-30%) or cardiac manifestations of NL (17%).<sup>9,11</sup> The maternal diagnosis was not associated with the outcome in a subsequent pregnancy.<sup>11</sup> The recurrence rate did not correlate with previous use of steroids or the antibody status of the mother. Death of the first child with cardiac NL was not predictive of recurrence of cardiac NL in a subsequent pregnancy. The risk of cardiac NL was similar between male and female children.<sup>11</sup>

Children who have had NL have no increased risk of



**Figure 13.2** The most common form of skin rash in neonatal lupus

developing another form of lupus erythematosus later in life. There is, however, a slightly increased risk on other autoimmune diseases. In a study 10 with 49 children with NL and 45 siblings without NL, six children had developed an autoimmune disease at the age of 14 years: juvenile rheumatoid arthritis (n=2), Hashimoto's thyroiditis (n=1), psoriasis and iritis (n=1), diabetes mellitus type I with psoriasis (n=1) and congenital hypothyroidism and nephrotic syndrome (n=1). All these six children had NL.

#### *Early detection of neonatal lupus*

Only women with antibodies to SSA/Ro and/or SSB/La run the risk of having a child with NL. They should be informed that the child may develop a skin rash or blood abnormalities after the birth, but that NL is usually quite harmless unless a heart block develops.

In order to detect any heart block, the foetal heartbeat can be checked between the 15<sup>th</sup> and 25<sup>th</sup> week of pregnancy by means of a foetal cardiogram. Advanced block and cardiomyopathy can occur within 1 week of a normal echocardiogram without initial first-degree block.<sup>2</sup> If the heartbeat remains normal between the 15<sup>th</sup> and 25<sup>th</sup> week of pregnancy, there is no risk of a heart block occurring after birth.

A female patient with antibodies to SSA/Ro and SSB/La has been described where the child developed a heart block in the 19<sup>th</sup> week of pregnancy. The mother was immediately treated with 4 mg/day

**Table 13.2 Clinical features of neonatal lupus (these do not all necessarily have to be present)**

- skin rash
- low counts of red or white blood cells or platelets
- (mild) hepatitis
- heart block
- other heart defects

dexamethasone, after which the child's heartbeat normalised within six weeks.<sup>1</sup>

Recently, a woman was described with high titer anti-Ro/SSA antibody who presented with fetal AV block (ventricular rate 61 beats per min (bpm)) and right ventricular myocardial echogenicity suggesting fibrosis at 18 weeks' gestation. A 2:1 AV block and intermittent periods of complete independence of atrial and ventricular rate were noted. Dexamethasone 4 mg per os was initiated. Within 1 week fetal heart rate increased to 120-125 bpm with first-degree AV block (PR interval 145 ms) and occasional premature atrial contractions. Sinus rhythm and normal systolic function and ductus venosus Doppler parameters with almost complete resolution of myocardial echogenicity were achieved by the third trimester. At the age of 3 years, the first-degree AV block persisted but cardiac function, growth and development were normal.<sup>8</sup>

Anti-SSA/Ro-associated third-degree congenital heart block is irreversible. Therefore, Friedman *et al* investigated early markers and effective therapy in 98 pregnancies of women with anti-SSA/Ro antibodies.<sup>2</sup> Echocardiograms were performed weekly from 16 to 26 weeks' gestation. PR intervals >150 ms were considered prolonged, consistent with first-degree block. Neonatal lupus developed in 10 cases; 4 were neonatal lupus rash only. Three fetuses had third-degree block; none had a preceding abnormal PR interval, although in 2 fetuses >1 week elapsed between echocardiographic evaluations. Tricuspid regurgitation preceded third-degree block in 1 fetus, and an atrial echodensity preceded block in a second. Two fetuses had PR intervals >150 ms. Both were detected at or before 22 weeks, and each reversed within 1 week with 4 mg dexamethasone. The ECG of 1 additional newborn revealed a prolonged PR interval persistent at

#### **First-degree AV block in neonatal lupus**

First-degree AV block in neonatal lupus may be reversible if prompt treatment is given to the mother with 4 mg dexamethasone daily.<sup>1,2,8</sup>

**Table 13.3 Classification of a number of a number of drugs according to (certain or probable) risk to the child in pregnancy**<sup>9</sup> *SEE WARNING ON THIS PAGE.*

<i>probable safe</i>	<i>risky</i>	<i>dangerous</i>
amitriptyline	chlorpromazine	chlorambucil
amoxicillin	cyclosporine	chloramphenicol
aspirin (applies to low dose only)	diazepam	cocaine
atenolol	haloperidol	cyclophosphamide
azathioprine	methotrexate	ergotamine
captotril	sulfasalazine	methotrexate
chloroquine	5-ASA	metoclopramide
chlorothiazide	temazepam	metronidazole
cimetidine <sup>1</sup>	tramadol	NSAIDs (all) <sup>b</sup>
colchicine		phenobarbital
co-trimoxazole		
dapsone		
hydroxychloroquine <sup>a</sup>		
nifedipine		
prednisolone		
propranolol		

<sup>a</sup> patients with Sjögren's syndrome are usually advised to stop taking hydrochloroquine, but patients with systemic lupus erythematosus should continue

<sup>b</sup> all prostaglandin synthesis inhibitors such as ibuprofen, naproxen, diclofenac etc. including selective cox-2 inhibitors are dangerous for the fetus as they may induce premature closure of the ductus arteriosus (Botalli's duct)

3 years despite normal intervals throughout gestation. No first-degree block developed after a normal ECG at birth. Heart block occurred in 3 of 16 pregnancies (19%) in mothers with a previous child with congenital heart block and in 3 of 74 pregnancies (4%) in mothers without a previous child with congenital heart block or rash. These data allow the conclusion that first-degree AV block in neonatal lupus may be reversible if prompt treatment is given to the mother with 4 mg dexamethasone daily.

### 3. Medication

Many medicines can better be avoided during pregnancy since it is not known for certain if they are safe for the child (see table 13.3).

Hydroxychloroquine (Plaquenil®) has been found to be safe during pregnancy and lactation but is usually stopped, unless the patient has systemic lupus erythematosus (SLE). Recently, English articles on hydroxychloroquine (HCQ) published between 1982-2007 were systematically reviewed.<sup>12</sup> In pregnant women, it was found that antimalarials, particularly HCQ, decrease lupus activity without harming the baby. It was concluded that HCQ should be given to most patients with SLE during the whole course of the disease, irrespective of its severity, and be continued during pregnancy. Common sense dictates that HCQ, despite it may be less necessary to continue it's use in less severe diseases than SLE (such as Sjögren's syndrome), its use during pregnancy in other diseases is safe too. Prednisolone and low dose aspirin can be taken if required. It is also preferable for pregnant patients to stop taking most other anti-inflammatory drugs and pilocarpine. *Generally speaking, all anti-inflammatory drugs from the prostaglandin synthesis inhibitor group (see chapter 5) should be avoided.* This

## WARNING

The information on the safety of drugs in pregnancy for the developing child is meant as background information.

*Do always consult your own physician for all questions on the safety of using drugs during your pregnancy.*

**Old drugs are safer than new drugs**

Drugs that have been on the market for a long time can on average be assumed to be safer than drugs that have been just a short time on the market. It may also be assumed that most side effects are known of drugs that have been on the market for a long time and are frequently used. The list of possible side effects is consequently longer than that for drugs that have been only recently introduced. A long list of possible side effects does not therefore necessarily mean that the drug is unsafe.

is especially true in the last three months of pregnancy as they can cause premature closure of the ductus arteriosus (Botalli's duct), probably mainly due to the cox-2 inhibiting effect (see chapter 5). The ductus arteriosus is a blood vessel that connects the aorta with the pulmonary artery and bypasses the still undeveloped lungs. Closure normally takes place directly after the birth. Closure before the birth leads to severe strain on the baby's heart because the blood is forced to circulate through the still undeveloped lungs.

**4. Thyroid disease and pregnancy**

Women on thyroid hormone replacement therapy need a 50% increase of their daily dose during their whole pregnancy to avoid negative effects of (subclinical) hypothyroidism on the developing child.

**B. LACTATION**

**Medication**

Medication should not be taken when breastfeeding unless essential and proven safe. It is important to prevent the baby from unnecessarily ingesting medication via the breast-milk. Some medicines are safe for adults but harmful to children. Since medicines can occur in breast-milk in high concentrations, the child ingests more than you would initially suspect. If medication is nevertheless necessary, the following points are important:

- use the safest effective medicine;
- take the medication immediately after breastfeeding the baby so as to ensure the longest possible time before the next feed;
- if possible have the concentration of the medicine in the baby's blood tested.

The use of hydroxychloroquine is considered to be safe during lactation.

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**Latest additions or modifications (date: dd.mm.yyyy)**

<i>date</i>	<i>addition/modification</i>	<i>page(s)</i>
12.01.2009	additional information on the safety of using hydroxychloroquine during pregnancy and lactation	112,113
26.01.2009	information on follow-up of children who have had neonatal lupus (ref. 10) paragraph (4) on thyroid replacement therapy during pregnancy.	118 119
16.08.2009	conversion to another DTP program	
01.10.2009	ref 11 recurrence rate cardiac manifestations of NL	112