Challenges of lupus pregnancies

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SLE primarily affects young females of childbearing age and fertility is generally conserved. SLE is a predominantly Th2-mediated disease and a progressive Th1/Th2 cytokine shift is seen in the fetal–maternal unit as well as in maternal circulation. Whether this fact affects pregnancy is unknown. Pregnancy represents a challenge for lupus patients and their physicians. However, the majority of SLE patients can now have successful pregnancies and deliver healthy babies, a result of our knowledge of the risks that SLE patients have to face during pregnancy, the preventive and therapeutic measures that we adopt, when necessary, and the close and appropriate rheumatological, obstetric and neonatal monitoring. All of these aspects are discussed in this review.

**Key words:** Pregnancy, Pregnancy outcomes, Systemic lupus erythematosus, Th1 and Th2 cytokines, Systemic lupus erythematosus activity, Congenital heart block.

**Introduction**

SLE is an autoimmune disease that affects various organs and tissues inducing inflammation and damage. SLE affects young females in childbearing age. Over the last decades, improvement of survival rate and quality of life in SLE patients has led to an increased number of pregnancies observed during the course of the disease.

In pregnancy, profound immune-endocrine changes occur. Hormonal modifications during pregnancy are regulated by the feto–placental unit and depend on interactions between mother and fetus [1]. The physiological increase of cortisol, progesterone and oestradiol during pregnancy may lead to Th2 cytokine polarization both at the feto-maternal interface and at the systemic level [2]. Indeed, the suppression of the immune response mediated by Th1 cytokines may be essential for fetal survival.

Some but not all investigators believe that some autoimmune diseases, such as SLE, which are mainly mediated by Th2 cytokines, tend to occur or relapse during pregnancy, whereas Th1-mediated disease, such as RA, tends to improve [2]. Other non-T-cell-based mechanisms for change in clinical course have been proposed. Because SLE is a multi-system, complex illness, pregnancy is a challenge for lupus patients and their physicians. This review is focused on the disease course, gestational outcome and management of patients with SLE during pregnancy.

**Effect of pregnancy on the disease**

Pregnancy is not uncommon in SLE patients, since the disease affects young females of childbearing age and fertility is generally conserved, except when renal function is seriously compromised (creatinine clearance <50 ml/min), the disease is very active, or when amenorrhoea has been induced by cytotoxic therapy (cyclophosphamide) [2].

One of the major risks for SLE mothers is the occurrence of a disease flare during pregnancy. However, whether or not SLE tends to flare more during pregnancy is still an unresolved issue. Up to now seven prospective comparative studies using non-pregnant SLE patients as controls have been published, but they do not allow a definite answer (Table 1). In fact, the conclusion of three of them was that SLE flares more during pregnancy [3–5], but the conclusion of the other four was quite the opposite, i.e. SLE does not flare more during pregnancy [6–9]. Notwithstanding the difference in terms of flare frequency between pregnant and non-pregnant SLE patients, the percentage of flare in all these studies was ~50%.

The risk of flare seems to depend on the level of maternal disease activity in the 6–12 months before conception. If SLE is active in that period, then the patient has a high risk of having a disease flare during pregnancy; if the disease is in remission then the risk is reduced [3]. Pregnancy should therefore be planned when SLE is in remission [10].

The second major risk of SLE relapse during pregnancy is glomerulonephritis [11]. The risk of flare is higher if glomerulonephritis is active at the time of conception, but it is high even when in remission. Two recent studies carried out on 102 pregnancies in 75 SLE patients who had had lupus nephritis before pregnancy but who were in remission at the time of conception, showed a proteinuric flare ranging between 45% and 50% of cases and a worsening of renal function in 17–21% of cases [9, 11]. Pre-eclampsia also increases proteinuria, making it hard to distinguish between pre-eclampsia and renal exacerbation.

Apart from glomerulonephritis, SLE flares during pregnancy and in post-partum are generally mild or moderate, with a predominance of cutaneous, articular and minor haematological manifestations (thrombocytopenia is common in all pregnancies) [3, 6, 7]. However, severe exacerbations of the disease, characterized by major organ involvement, have been reported with a frequency varying between 5% and 46% in different studies [3, 10]. Maternal death may also occur, although nowadays only very rarely [12].

The definition of SLE activity criteria in pregnancy requires care. Some typical clinical manifestations of pregnancy can match some symptoms of the active disease: arthralgias, myalgias, erythema on the malar eminences and palms of the hand, hair loss, oedema of the face, hands and of the lower limbs, and carpal tunnel syndrome. Some laboratory parameters that are useful in evaluating SLE activity are modified during pregnancy: ESR increases and haemoglobin decreases due to haemodilution, while the serum levels of C3 and C4 increase due to increased liver synthesis induced by oestrogens. In SLE patients with inactive disease, C3 and C4 increase, as it occurs in pregnancies of healthy subjects (except in cases of congenital deficiency); however, when disease is active they decrease. Nevertheless, since the baseline values are higher, they can result within the normal range. Therefore, in a pregnant patient with SLE, the observation of C3 and/or C4 values within normal range cannot exclude the possibility that the disease is active. In some cases of toxaemia or other hepatic diseases of pregnancy, complement levels fall; hence, low complement levels do not always indicate disease activity.
Recently, activity indexes used in non-pregnant SLE patients, including the ECLAM, SLEDAI, SLAM and Lupus Activity Index (LAI) values, have been adopted for pregnancy [13–15]. Both SLEDAI and LAI have been validated in SLE pregnant patients [15] showing a sensitivity of 93% and a specificity of 98%.

### Timing of flares in SLE patients during pregnancy

Disease flare can occur at any time during pregnancy and post-partum without any clear pattern. However, some recent prospective studies report a low percentage of flares in the third trimester of SLE pregnancy [3, 6, 16]. Doria et al. [13, 17] has recently evaluated the serum level variation of steroid hormone and some cytokines involved in humoral immune response during pregnancy and post-partum in SLE patients and in healthy subjects, as controls. Among steroid hormones, oestradiol and progesterone showed the most relevant alterations since both were reduced in SLE pregnant women in the second and even more in the third trimester in comparison with normal pregnant women, periods in which these hormones are predominantly secreted by the placenta [13]. Thus, the reduction in their serum concentration might suggest placental damage and/or dysfunction. Among cytokines, the most relevant modification seems to be the lower than expected increase of IL-6 in the third trimester of gestation. The blunting of IL-6 might reflect the lower levels of oestrogens in the last trimester of pregnancy and might account for the low percentage of SLE relapses reported in the third trimester of pregnancy by some authors [3, 6, 17].

### Effect of SLE on pregnancy

Pregnancy of SLE patients can be complicated by a number of obstetric and neonatal problems [18]. Besides an increased rate of pregnancy losses (spontaneous abortion or intrauterine fetal death), the most frequent fetal complications observed are premature birth, intrauterine growth restriction (IUGR), premature rupture of membrane and precocious premature rupture of membrane, while pre-eclampsia/eclampsia seems to be the most frequent obstetric complication.

During the pre-conception counselling each patient should be advised about her possible risk. Glomerulonephritis, especially Class III–IV, should be regarded with particular attention, since severe active renal disease is associated with pregnancy loss and premature delivery. These fetal complications may be consequences of hypertension and pre-eclampsia/eclampsia that can occur in over 35% of patients with lupus glomerulonephritis [19].

Besides disease activity, another major risk factor for the outcome of pregnancy in SLE patients is the presence of autoantibodies highly associated with fetal damage. Among these, anti-Ro/SS-A and anti-La/SSB antibodies, responsible for neonatal lupus, will be treated in the “ad hoc” article of this issue [20]. The aPLs are the major risk factor for pregnancy loss in patients with SLE and in those with primary APS. These antibodies play a direct pathogenic role not only by aPL-mediated thrombophilia of the placenta, but also by the direct effect of antibodies on trophoblast possibly through exposed anionic phospholipids and/or adherent β2 glycoprotein (β2GPI), resulting in altered trophoblast intercellular fusion, gonadotropin secretion and trophoblast invasiveness [21]. By studying pregnancies in patients with SLE, prospectively followed and treated during gestation, Tincani et al. [22] has shown that positive aPLs are predictive of both premature births and pre-eclampsia, but not of pregnancy loss. This finding suggests that correct treatment, together with careful rheumatological and obstetric follow-up and high-quality neonatal care, tend to improve the outcome of pregnancy in patients with APS also when it occurs within SLE [22]. Early onset, severe pre-eclampsia complicated by haemolysis, elevated liver enzymes and low platelets (HELLP syndrome) also occurs in pregnant patients with aPL and this fact is not surprising considering that HELLP and APS may have similar pathogenic mechanisms [23]. A recent review reported 46 pregnancies in women affected by HELLP and APS; this condition can precede APS clinical manifestations. In HELLP in particular, thrombocytopenia can occur as early as 15–20 weeks’ gestation and may progress rapidly. Besides thrombocytopenia, other symptoms of pre-eclampsia and HELLP such as anaemia, proteinuria and hypertension may look like active SLE, supporting the need for careful clinical/serological observation. These two disorders that may not be able to be differentiated can also coexist. Abnormalities that are suggestive of disease flare include C3 and C4 decrease, high titre of anti-double stranded DNA antibodies, active urine sediment and the coexistence of active SLE manifestations in other organs. Today, it is still unknown how high the risk of recurrence HELLP syndrome is. According to the ‘experts’ opinion the risk can be as high as 30–50% or as low as 25% [24].

Taking into account prematurity and IUGR, the frequent exposure of the fetuses to the drugs used to care maternal disease and the possibility of a genetic transmission of autoimmune diseases, it is of the greatest interest to collect information on the long-term outcome of children born to SLE patients. Unfortunately, data in this area are lacking. According to several reports, children born of SLE pregnancies have an increased prevalence of learning disabilities when examined between 7 and 16 yrs of age. Among these, dyslexia is the most common. Two different reports find an association of dyslexia with maternal anti-Ro/SS-A antibodies and aPL, respectively [25, 26]. According to these findings, a long-term neuropsychological follow-up of children born to SLE patients is recommended. Early diagnosis of learning disabilities could help to overcome difficulties that eventually arise during school years.

### Treatment issues

Prospective controlled studies on the safety of anti-rheumatic therapy in lupus pregnancies do not exist. Information has accrued through collective experience that, as a rule, is unable to distinguish between disease- and medication-associated complications. In many if not most cases, discontinuation of a medication because of pregnancy may lead to more damage to the mother and fetus from worsening of maternal disease. Consensus forums and mining of public databases provide the limited data that support the conclusions that follow. A detailed review of this issue was published in 2006 and is updated elsewhere in this volume [27, 28].

Treatments used during SLE pregnancy include anti-inflammatory drugs, anti-malarials, immunosuppressives, biologicals and anti-coagulants.

### NSAIDs and anti-malarials

NSAIDs may impair fertility, although the risk is low. At moderate doses NSAIDs are generally not problematic in early pregnancy, but in late pregnancy they may lead to constriction of the fetal ductus arteriosus, which may be lethal to the fetus if the

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**Table 1. Controlled, prospective studies on lupus flares during pregnancy**

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of pregnancies</th>
<th>Controls</th>
<th>Pregnancy flares (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lookshitz et al. [4]</td>
<td>33</td>
<td>Matched controls</td>
<td>27</td>
</tr>
<tr>
<td>Mintz et al. [3]</td>
<td>92</td>
<td>Non-pregnant patients</td>
<td>59</td>
</tr>
<tr>
<td>Urowitz et al. [5]</td>
<td>79</td>
<td>Matched controls</td>
<td>70</td>
</tr>
<tr>
<td>Tandon et al. [9]</td>
<td>78</td>
<td>Non-pregnant patients</td>
<td>45</td>
</tr>
</tbody>
</table>

Increased flare rate in pregnancy:

- Petri et al. [6] | 40 | Post-pregnancy course | 60 |
- Wong et al. [8] | 29 | Non-pregnant patients | 58 |
- Rutz-istrafoza et al. [7] | 78 | Post-pregnancy course | 65 |
drug is not immediately discontinued. NSAIDs are generally safe during breastfeeding. Anti-malarials are generally safe. Instances of fetal blindness or deafness appear to be rare [29].

**Corticosteroids**

Prednisone and the non-fluorinated other corticosteroids may lead to a slight increase in cleft palate and fetal growth restriction. These drugs at low doses do not reach the fetus. Fluorinated corticosteroids (dexamethasone or betamethasone) do reach the fetus and potentially cause typical steroid side-effects. Corticosteroids given during pregnancy may increase the risk of pregnancy-induced diabetes or hypertension. ‘Bolus’ or ‘pulse’ corticosteroids, usually given intravenously as 1000 mg methylprednisolone over a short period of time, do reach the fetus and are capable of causing acute vasospasm, abrupt hypertension and potential placental ischaemia, and hence should be avoided. Prednisone is safe during breastfeeding.

**Immunosuppressive drugs**

Among the small-molecule immunosuppressive drugs, AZA/6-mercaptopurine is generally safe, though fetal malformations have been reported from its use. Ciclosporin reaches the fetus but does not appear to be teratogenic. MTX, cyclophosphamide, mycophenolate mofetil and LEF are teratogenic; MTX and cyclophosphamide are abortifacient. None are recommended during lactation, but a few case reports testify to the possible safety of AZA, ciclosporin and tacrolimus in nursing mothers.

**Biologicals**

Biological agents are potentially safer than small molecules, in part because immunoglobulins are not transmitted to the fetus until relatively late in pregnancy [30, 31]. Intravenous immunoglobulin, etanercept, infliximab and anakinra carry acceptable United States Food and Drug Administration (FDA) ratings (B) for use in pregnancy. Less information is available about adalimumab, but it probably behaves similarly to infliximab. There is no reliable information about abatacept in humans. Rituximab is potentially less safe because reversible fetal cytopenias, including B-cell depletion have occurred in infants of mothers who are given this drug during pregnancy. A recent alert about the possible association of VATER syndrome (vertebral anomalies, anal atresia, tracheo-oesophageal fistula/atresia, renal and radial anomalies) with TNF inhibitors is of uncertain significance [32].

**Miscellaneous drugs**

The class of bisphosphonates, used for osteoporosis, carries FDA rating C (insufficient information), but deposition in fetal bones is possible and these drugs should be avoided. Teriparatide received a similar rating; since it is responsible for fluctuations of plasma calcium levels, and since it causes osteosarcomas in growing rodents, it, too, should be avoided. Among anti-coagulants used for patients with prothrombotic disorders, warfarin is teratogenic. In some countries, but not in the United States, its use is permissible after the first trimester. In the first trimester and throughout pregnancy in the United States, heparins are preferred. Theoretically, heparins may be more effective than other anti-coagulants because they inhibit complement activation and may be therapeutic at sub-anti-coagulant doses [33]. Direct thrombin inhibitors are probably safe. Colchicine is contraindicated.

In lupus as in any rheumatic illness, planning for a pregnancy is important and prospectively changing treatment to the least toxic effective drug is wise. In contrast, reflex discontinuation of an effective therapy because of recognition of pregnancy (without continuing treatment with another drug) often results in intolerable exacerbation that is both painful and threatening to the mother and risky for the fetus because of the mother’s illness.

Treating physicians should recognize the extremely limited quality and quantity of information about experience in pregnancy with drugs used for rheumatic diseases. In addition, many of these drugs, particularly the immunosuppressive drugs, impair both female and male fertility. Treating physicians should also be aware that maternal metabolism increases by approximately one-third during pregnancy, as obviously does weight; dose adjustments may therefore be required. Finally, the pregnancy complications of pre-eclampsia, HELLP syndrome, cholestasis and fatty liver of pregnancy alter hepatic or renal metabolism or both and will necessitate dose changes if they occur.

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**References**