Systemic Lupus Erythematosus and Antiphospholipid Syndrome during Pregnancy: Maternal and Fetal Complications and their Management

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Systemic lupus erythematosus affects mostly young women. Despite this, the interrelationship between SLE and pregnancy has remained poorly understood for years. Fear of maternal or fetal complications has often resulted in advice against pregnancy. Since the mid-seventies, an increasing number of authors are providing specific care for pregnant women with SLE. Their experience over the years has demonstrated that pregnancy is not only possible in patients with lupus, but also usually successful. Moreover, this experience has contributed to better knowledge of the effects of pregnancy and lupus on each other.

This review is based in part on our 10 year experience in the Lupus Pregnancy Clinic at St. Thomas’ Hospital. More than 300 women with SLE, antiphospholipid syndrome and other systemic autoimmune diseases have been treated during this period. We describe the maternal and fetal complications of lupus pregnancies and provide practical guidelines for management.

Maternal Complications

Pregnancy is a period of important changes in the mother’s body, all directed to allow the normal development of the fetus. Among them, adaptations in the immune and clotting systems may modify the course of SLE and APS. Specifically, disease activity and the tendency to thrombosis may be affected.

Effects of pregnancy on SLE activity

During pregnancy, the growing embryo behaves as an allograft, without triggering any response from the maternal immune system [1]. Fetal blood cells have been found in the maternal circulation [2], which implies that this immuno-tolerance is not limited to the placenta. Indeed, the synthesis of interleukin 10 and 4 — two of the main Th2 cytokines — increases during pregnancy whereas Th1 cytokines are inhibited. These adaptations may be regulated by sex hormones, though the relative contribution of estrogens, progesterone and prolactin is still a matter of debate. Thus, pregnancy can be considered a Th2 process from the immunological point of view [1].

SLE is a Th2 disease characterized by the overproduction of autoantibodies that may mediate organ damage, in contrast to rheumatoid arthritis where joint destruction is mostly cell-mediated — the typical Th1 mechanism. Given the well-known beneficial effect of pregnancy on the course of rheumatoid arthritis, we could expect the contrary with SLE.

Several controlled studies have focused on the effect of pregnancy on SLE activity [6–8], with somewhat conflicting results [Table 1]. The main reason for the heterogeneity is the absence of a common tool to determine the presence of lupus flares during pregnancy. Some studies have used validated scales such as LAI and SLEDAI, but these scales have not been tested in pregnant patients. Low grade proteinuria, edema, bland joint effusions, joint pains, fatigue, thrombocytopenia and rash are all common during pregnancy and can be confused with manifestations of lupus activity. Nonetheless there are points in common among the studies.

Whatever the controlled studies concluded, the frequencies of flare found in pregnant patients were generally similar [see Table 1]. The figures are less constant if we also take into account the uncontrolled prospective series that have been published [9–17]. However, low frequencies of SLE flare were mainly found in the studies that: a) had a high number of early miscarriages [9,10], b) excluded the puerperium from the follow-up [16], and c) included only cases of mild, long-term, well-controlled lupus [12,17]. Such studies are marked * in Table 2. The remaining papers, all including unselected pregnant populations with less than 20% miscarriages, showed frequencies of flare very close to those found in controlled studies. Accordingly, 60 to 65% of unselected women will have at least one SLE flare if their pregnancy does not result in early miscarriage. In other words, 0.07 to 0.08 flares per
patient-month can be expected in this group. This frequency of flare is probably higher than in non-pregnant lupus patients [18]. Conversely, patients with mild long-term controlled disease are at much lower risk, and short pregnancies are also less likely to include a flare up because the period at risk is also shorter. Interestingly, our own data show that patients with pregnancies of less than 28 weeks duration are also less prone to flare during the puerperium than women with longer pregnancies, and that the puerperium is also a high risk period for women without SLE activity antenatally [19].

Regarding SLE activity, all the studies show that lupus flares occurring during pregnancy are predominantly mild or moderate and affect mostly the skin and joints [18]. Severe visceral involvement, i.e., renal or neurological, is more the exception than the rule and does not occur with higher frequency than in non-pregnant patients. The factors that could predict SLE flares during pregnancy are not yet identified. However, we believe that recent nephritis may increase the risk of lupus reactivation.

In conclusion, a lupus flare can be expected in two out of every three women during pregnancy and the puerperium. Patients with mild and well-controlled disease are more likely to have an uneventful pregnancy from the lupus point of view. Close maternal monitoring should extend into the puerperium of every patient. Fortunately, most of the flares are mild/moderate and easy to control using non-steroidal anti-inflammatory drugs, hydroxychloroquine or low dose steroids.

Thrombotic complications
Normal pregnancy is a high risk period for thrombosis. Some physical factors, including the compression of the vena cava by the enlarged uterus, causing venous stasis in the lower limbs, or the relative immobility, account in part for this increased risk. In addition, several changes in the maternal clotting system, probably directed to avoid massive blood loss during delivery, also play a role. For instance, there is an increase in the levels of factor II, VII and X, as well as in the generation of thrombin. Conversely, protein S levels fall during pregnancy. As a result, venous thromboembolic events are the leading cause of maternal mortality in the UK. The general population is also at an increased risk of stroke during pregnancy and the puerperium.

This is very relevant to lupus, specifically to patients with antiphospholipid antibodies. APS, or Hughes’ syndrome, is a recognized cause of recurrent arterial and venous thrombosis and requires high grade long-term anticoagulation. Recurrent pregnancy loss is another feature of the syndrome, leading to the referral of such patients to high risk combined medical/obstetric clinics such as ours.

Thrombosis can complicate pregnancy in aPL-positive women. At present, most patients attending our lupus pregnancy clinic are known to have the syndrome due to previous manifestations. Similarly, most series include aPL-positive women who are already treated with heparin, aspirin or both. Despite this, thrombotic complications do not occur with higher frequency than in non-pregnant patients. The factors that could predict SLE flares during pregnancy are not yet identified. However, we believe that recent nephritis may increase the risk of lupus reactivation.

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still occur. Most cases are in aspirin-only treated women [20,21] but some patients given unfractionated heparin also have clots [21].

The recent advent of low molecular weight heparins may substantially change the picture. Compared with unfractionated heparin, LMWHs have higher antithrombotic to anticoagulant ratios, higher bioavailability and a more predictable antithrombotic effect, and seem to be safer too. Series including women at high risk for thrombosis (including aPL-positive patients) have had very good results using LMWH, with almost complete absence of thromboembolic events and hemorrhagic complications. In a recent systematic review of the available evidence that analyzed 486 pregnancies (163 with aPL or other autoantibodies) treated with LMWHs (nadroparin, enoxaparin, dalteparin, reviparin and tinzaparin) as the only anticoagulant, this group of drugs was shown to be very effective, with only 3 cases of thromboembolic complications [22]. On the other hand, the subgroup of patients with arterial disease, mainly stroke, may be better controlled with warfarin than with LMWH after fetal organogenesis is completed (warfarin is teratogenic, and is contraindicated during early pregnancy). In our experience, the switch to oral anticoagulation in some of our patients stopped recurrent transient ischemic attacks that were occurring despite treatment with dalteparin [23]. Women with arterial thrombosis are identified as high risk in our unit, both in terms of maternal and fetal outcomes. Thirteen patients with APS (primary and secondary to SLE) and a previous history of stroke suffered further cerebral ischemic events in 42% of the subsequent pregnancies. Women having a pregnancy within 18 months of a stroke also had a higher risk of pregnancy loss compared with the rest of the group [24]. These data point to a subgroup of patients in whom pregnancy must be more closely and more aggressively managed or, according to some authors, avoided.

Fetal Complications

Lupus pregnancies also put the infant at high risk. Several factors may compromise the normal growth and development of the fetus, specifically maternal lupus activity and the presence of some maternal autoantibodies, mainly aPL, anti-Ro and anti-La antibodies.

Maternal SLE activity during pregnancy

The effect of maternal lupus activity on the developing fetus has been studied in most prospective series. Miscarriage and fetal loss has not been more frequent among women with lupus flares antenatally than in those without [18]. The immediate conclusion could be that the occurrence of lupus flares in the mother has nothing to do with fetal well being. However, things are not so simple. First, both Mintz et al. [4] and Petri et al. [25] have shown that SLE activity in the mother correlates with an increase in prematurity. One of the reasons may be the need to deliver women who have severe SLE manifestations in order to treat them with intensive immunosuppressive regimes (for instance, cyclophosphamide pulses). In addition, doses of prednisolone higher than 20 mg/day are strongly associated with prematurity [25]. Second, it was suggested in 1992 that active nephritis could be a factor for obstetric complications [15]. In our series, all eight women with active nephritis ended their pregnancies preterm, with the final result of four intrauterine deaths and one neonatal death of a very premature baby. These adverse experiences have been confirmed by a recent work of Rahman et al. [27] who prospectively studied which factors correlated with adverse fetal outcomes in a series of women with SLE. The final regression model demonstrated active nephritis to be an independent risk factor for fetal mortality. Finally, previous renal disease has also been found to correlate with adverse pregnancy outcomes, mainly prematurity, in three retrospective series [reviewed in 18]. The finding by Petri and coworkers [25] that maternal arterial hypertension and proteinuria are predictors for preterm birth may explain in part the influence of previous inactive nephritis on the developing fetus.

Antiphospholipid antibodies

Recurrent pregnancy loss is one of the main features of APS. Since Hughes’ initial description in 1983, the spectrum of aPL-related obstetric complications has widened. The last consensus classification criteria for this syndrome, published in 1999 [28], include the following obstetric criteria: a) the presence of three or more consecutive unexplained miscarriages (less than 10 weeks), b) the presence of at least one unexplained fetal death (more than 10 weeks), and c) the delivery of at least one premature baby at or before 34 weeks due to severe preeclampsia or eclampsia or severe placental insufficiency. Women with aPL (lupus anticoagulant or anticardiolipin IgG or IgM at medium/high titers, positive on two occasions at least 6 weeks apart) and any of the above clinical criteria are at high risk of subsequent pregnancy losses if untreated. Typical figures in this group show more than 80% pregnancy failure [29]. In a similar way, the presence of aPL is a strong predictor of a bad obstetric history in patients with SLE. However, in daily clinical practice we often find healthy women with positive antibodies without any previous obstetric or thrombotic complications. The significance of aPL in this setting is far less clear. The prevalence of aPL in the general obstetric population is generally below 7% [30]. Even among patients with recurrent pregnancy losses attending specialist clinics, the prevalence of aPL is in the range of 5% [20]. One study has found the frequency of pregnancy loss to be very low in aPL-positive women without previous history of miscarriage, thrombosis or thrombocytopenia [31]. That is, most otherwise healthy patients with incidental aPL have uneventful pregnancies. Accordingly, the predictive value...
of aPL for pregnancy complications is very low in the general population. On the other hand, the presence of other manifestations of APS (mainly thrombosis), and especially a previous history of recurrent miscarriage, make the finding of aPL extremely significant.

APS is related to all forms of fetal complications: first trimester miscarriage, fetal death, prematurity and low birth weight [20,21,32]. Fetal loss is, however, the most characteristic obstetric feature of APS. Although rarely seen in women with recurrent miscarriage of other etiology, up to 50% of patients with APS experience fetal loss in the second or third trimester [33]. The mechanisms of this late pregnancy loss seem to be related to placental insufficiency, as thrombosis of the placental vasculature and infarctions are common pathologic findings in this group of patients [34].

Four groups have published results with large numbers of pregnant APS patients [20,21,35,36]. All women received at least aspirin. Older series [20,21] included patients treated with prednisone, a practice already abandoned by most centers in the management of APS, although many of our patients still take prednisone for SLE. No patients received steroids in the two more recent series, due in part to the fact that SLE was uncommon in both. All women were given heparin in the St. Mary’s group [36], but 70% of patients in the Liverpool series received aspirin only [35]. The final results were similar in all four series in terms of successful pregnancies, and showed marked improvement, ranging from 27 to 57%, compared to previous obstetric outcomes. Despite this, the frequency of fetal complications was also high, although some differences were found that underlined the heterogeneity of aPL-positive women in the different clinics. The most frequent fetal complication was prematurity, sometimes due to preterm spontaneous labor but also to spontaneous premature rupture of membranes, placental abruption or maternal preeclampsia [20,21,36]. Some pregnancies were complicated with intrauterine growth restriction [20,21,35,36]. These facts reinforce the idea that even treated pregnancies are high risk in women with APS, and should be managed accordingly. Indeed, most experts agree that a substantial part of the improved results in these patients is due to the better obstetric and fetal surveillance.

Anti-Ro and anti-La antibodies and neonatal lupus syndrome
Neonatal lupus erythematosus is considered a model of passively acquired autoimmunity, in which maternal autoantibodies cross the placenta and result in fetal tissue damage [37]. More precisely, this syndrome is strongly linked to the presence of anti-Ro and anti-La in maternal blood [37]. Neonatal lupus appears in 1 to 5% of the offspring of Ro-positive mothers [37]. The risk increases substantially to around 20% if a previous baby was affected [37,38].

Related clinical manifestations are diverse. Photosensitive subacute cutaneous lupus-like rash is the most common, accounting for more than 50% of neonatal lupus cases [38]. Rash usually becomes manifest within the first weeks of postnatal life and subsides in most cases within 6 months, coincident with the clearing of maternal antibodies from the baby’s circulation [38]. The second in frequency and most feared complication of neonatal lupus is congenital heart block. This is a serious condition, since around 60% of children may require pacemakers, and as many as 15–22% may die [37]. Both forms of neonatal lupus can occur separately or together, although in our experience the coexistence of both is rare. Other less frequent manifestations are thrombocytopenia and cholestatic hepatitis, both of which are usually reversible [37].

Complete congenital heart block is irreversible. However, some cases of incomplete heart block have been successfully treated in utero with dexamethasone, a corticosteroid that crosses the placenta [39]. Therefore, serial fetal echocardiograms between 16 and 30 weeks, the period when most cases of congenital heart block occur, is mandatory in all anti-Ro and/or anti-La positive women.

Preeclampsia
Preeclampsia is a severe form of pregnancy-induced hypertension. It usually presents during the third trimester but may be seen at any time after 20 weeks gestation. It is defined as the presence of blood pressure persistently above 140/90 mmHg or an increase of at least 30 mmHg systolic or 15 mmHg diastolic over first trimester values, plus proteinuria of at least 300 mg in 24 hours [40]. To date, there is no reliable method of preventing preeclampsia.

Preeclampsia is associated with major morbidity in both the mother and the baby [40]. It can evolve into a multi-systemic disease, with renal failure and occasionally hemolysis, thrombocytopenia and liver involvement (the so-called HELLP syndrome), or it may affect the central nervous system, with brain edema and seizures (eclampsia), any of which may result in high maternal mortality. On the fetal side, any form of hypertension is a predictor for prematurity and intrauterine growth restriction [25,27]. Preeclampsia and HELLP have both been linked to the presence of aPL [41,42]. Previous renal involvement may also be a risk factor for arterial hypertension and preeclampsia [18]. Table 3 shows the frequency of pregnancy-induced hypertension and preeclampsia or eclampsia in the various series of women with SLE or APS. The frequency of hypertensive complications was in the range of 40–50% in most series with a high number of patients with aPL or previous nephritis.
A crucial point regarding preeclampsia and SLE is to differentiate the former from a flare of lupus nephritis, since both are characterized by proteinuria. Hypertension, edema and renal failure may also be common features. However, the therapeutic approach to each is rather different: immunosuppressive drugs for lupus nephritis, and delivery for preeclampsia. Unfortunately, no single test is available. The finding of other signs of SLE activity — whether clinical (arthritis, rash, fever) or biochemical (raised anti-DNA levels, low C3 or C4) — or the presence of urinary casts, all point to the diagnosis of SLE renal involvement. Elevation of serum uric acid levels, due to its decreased renal clearance, often occurs in preeclampsia. However, in the common setting of an unclear diagnosis, empirical therapy may be appropriate.

Management

Pregnancy in most women with SLE or APS is successful nowadays. This is an important message, but the degree of success depends to a great extent on accurate monitoring and management. Ideally, a combined team including obstetricians and lupus specialist should follow all patients. The management guidelines of the St. Thomas’ Lupus Pregnancy Clinic, based on our large experience as well as on the available evidence from other centers, has recently been updated.

General monitoring

All women should be booked early in pregnancy. A complete autoantibody profile, including anti-DNA, anti-Ro, anti-La, and aPL (anticardiolipin, IgG and IgM and lupus anticoagulant) should be available preferably before, but at least in early pregnancy. During pregnancy only anti-DNA levels should be checked regularly, along with C3 and C4, since they are useful tools for monitoring SLE activity.

Women should be seen more frequently as their pregnancy advances. Our scheme of visits is as follows: monthly until the 32nd week, fortnightly until the 36th week, and then weekly until delivery. Blood pressure and the presence of protein in the urine must be monitored at each visit. Uterine and umbilical artery Doppler blood flow analyses at 20 and 24 weeks, and fetal cardiac scans if mothers are anti-Ro/La-positive [37], are strongly recommended in addition to routine ultrasound scans to evaluate fetal growth. Women should be followed closely until at least 8 weeks post-partum because of the risk of flare.

A list of drugs that are permitted, safe, to be avoided during pregnancy, and likely to be used in SLE and APS patients, is given in Table 4. Breast-feeding is allowed in women taking hydroxychloroquine, aspirin, LMWHs, warfarin or prednisolone at a dose below 25 mg/day. Women taking azathioprine are advised against breast-feeding due to the excretion of the drug in mother’s milk and the subsequent risk of immunosuppression in the baby.

### Table 3. Frequency of pregnancy-induced hypertension and preeclampsia/eclampsia in prospective series of pregnant patients with SLE or APS

<table>
<thead>
<tr>
<th>Author [ref]</th>
<th>Year</th>
<th>aPL</th>
<th>Previous nephropathy</th>
<th>Hypertension</th>
<th>Preeclampsia/eclampsia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nossent [13]</td>
<td>1990</td>
<td>43%</td>
<td>13.5%</td>
<td>23%</td>
<td>13%</td>
</tr>
<tr>
<td>Branch [20]</td>
<td>1992</td>
<td>100%</td>
<td>NA</td>
<td>NA</td>
<td>51%</td>
</tr>
<tr>
<td>Tincani [15]</td>
<td>1992</td>
<td>19%</td>
<td>33%</td>
<td>8%</td>
<td>4%</td>
</tr>
<tr>
<td>Derksen [9]</td>
<td>1994</td>
<td>44%</td>
<td>40%</td>
<td>NA</td>
<td>26%</td>
</tr>
<tr>
<td>Lima [26]</td>
<td>1995</td>
<td>49%</td>
<td>16%</td>
<td>42%</td>
<td>5%</td>
</tr>
<tr>
<td>Lima [21]</td>
<td>1996</td>
<td>100%</td>
<td>NA</td>
<td>23%</td>
<td>17%</td>
</tr>
<tr>
<td>Granger [35]</td>
<td>1997</td>
<td>100%</td>
<td>NA</td>
<td>NA</td>
<td>3%</td>
</tr>
<tr>
<td>Backos [36]</td>
<td>1999</td>
<td>100%</td>
<td>0%</td>
<td>6%</td>
<td>12%</td>
</tr>
<tr>
<td>Carmona [17]</td>
<td>1999</td>
<td>35%</td>
<td>16%</td>
<td>11%</td>
<td>7.5%</td>
</tr>
</tbody>
</table>

NA = not available

### Table 4. Summary of drugs permitted and to be avoided during pregnancy

<table>
<thead>
<tr>
<th>Permitted</th>
<th>To be avoided</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immunosuppressive drugs</strong></td>
<td></td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Cyclophosphamide</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Methotrexate</td>
</tr>
<tr>
<td><strong>Corticosteroids</strong></td>
<td></td>
</tr>
<tr>
<td>Prednisone/prednisolone</td>
<td>Dexamethasone*</td>
</tr>
<tr>
<td>Methyl-prednisolone</td>
<td></td>
</tr>
<tr>
<td><strong>Antimalarials</strong></td>
<td></td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>Chloroquine</td>
</tr>
<tr>
<td><strong>Antihypertensive drugs</strong></td>
<td></td>
</tr>
<tr>
<td>Methyl-dopa</td>
<td>ACE inhibitors</td>
</tr>
<tr>
<td>Labelalol</td>
<td>Diuretics</td>
</tr>
<tr>
<td>Nifedipin</td>
<td></td>
</tr>
<tr>
<td><strong>Anticoagulant and anti-aggregant drugs</strong></td>
<td></td>
</tr>
<tr>
<td>Heparin and LMWHs</td>
<td>Warfarin</td>
</tr>
<tr>
<td>Aspirin</td>
<td></td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
</tr>
<tr>
<td>Vitamin D</td>
<td>NSAIDs</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Immunoglobulins</td>
</tr>
</tbody>
</table>

*Except for in utero treatment of fetal myocarditis, hydrops fetalis or immature babies. ACE = angiotensin-converting enzyme, LMWHs = low molecular weight heparins, NSAIDs = non-steroidal anti-inflammatory drugs.
Control of SLE activity
Two recent in-depth reviews address the effects of immunosuppressive drugs during pregnancy [43,44]. It is our policy to change preconception maternal treatment as little as possible. We do not add prophylactic prednisolone to the treatment, since there is no evidence that this lowers the frequency of flares, and its side effects during pregnancy are substantial [18]. On the other hand, hydroxychloroquine has been shown to be safe for the fetus [45], and its withdrawal can result in an SLE flare [46]; accordingly, we maintain this drug during the whole pregnancy as required. SLE flares are treated according to their severity. Rash and arthritis can be managed with non-steroidal anti-inflammatories, which should be stopped in late pregnancy due to their interference with delivery and the risk of premature closure of ductus arteriosus [47], as well as with low dose prednisolone (up to 10 mg/day) or hydroxychloroquine.

More serious manifestations, like vasculitis, nephritis or neuropsychiatric involvement, require higher doses of prednisolone, pulses of methyl-prednisolone or neuropsychiatric involvement, require higher doses of prednisolone, pulses of methyl-prednisolone or hydroxychloroquine. Two recent in-depth reviews address the effects of immunosuppressive drugs during pregnancy [43,44]. It is our policy to change preconception maternal treatment as little as possible. We do not add prophylactic prednisolone to the treatment, since there is no evidence that this lowers the frequency of flares, and its side effects during pregnancy are substantial [18]. On the other hand, hydroxychloroquine has been shown to be safe for the fetus [45], and its withdrawal can result in an SLE flare [46]; accordingly, we maintain this drug during the whole pregnancy as required. SLE flares are treated according to their severity. Rash and arthritis can be managed with non-steroidal anti-inflammatories, which should be stopped in late pregnancy due to their interference with delivery and the risk of premature closure of ductus arteriosus [47], as well as with low dose prednisolone (up to 10 mg/day) or hydroxychloroquine.

More serious manifestations, like vasculitis, nephritis or neuropsychiatric involvement, require higher doses of prednisolone, pulses of methyl-prednisolone – which we do not use very often – and the early introduction of azathioprine to allow a rapid reduction of steroid dosage. Should this not control disease activity, pregnancy termination and more aggressive immunosuppressive treatment is the next step. Cyclophosphamide and methotrexate are absolutely contraindicated during pregnancy. Cyclosporine, which is safe during pregnancy, is recommended by some authors for treating nephritis when azathioprine has failed. This can be considered in individual cases with severe but non-life-threatening disease.

Antiphospholipid syndrome
Treatment of pregnant women who have APS is directed towards prevention of miscarriage and thromboprophylaxis. However, not all patients with APS are at risk of both complications [32]. Therefore, decisions regarding treatment mostly depend on previous clinical manifestations. The two main drugs used during pregnancy in women with APS are low dose aspirin (75–100 mg/day) and heparin, since prednisone does not seem to play a major role in APS [48,49]. Indeed, women treated with corticosteroids for pregnancy losses experience higher rates of prematurity, hypertension and diabetes [50]. Our results with aspirin alone in patients without a history of thrombosis have been good, showing a 71% success rate [21]. Other authors have reported similar figures [35,49,51]. However, recent studies have shown the combination aspirin-(unfractionated) heparin to be superior to aspirin alone [52,53], and good results have also been reported using unfractionated heparin at anticoagulant doses (as controlled with activated partial thromboplastin time) without aspirin [54,55]. Some heterogeneity in the populations studied, mainly in the severity of APS and the levels of aPL, makes it difficult to reach any definitive conclusion. The comparison of aspirin versus placebo has for obvious reasons not been done, and none of the above studies have used LMWHs, which are becoming widely used because of their convenience and safety profile. Therefore, although both aspirin and heparin are useful for treating pregnant women with APS, the optimal combination for each subgroup of patients is not yet defined. Accordingly, the protocols of each individual clinic very much depend on personal experience.

Our current practice is as follows:

- For aPL-positive women without any history of thrombosis or pregnancy loss, we recommend aspirin because of its low toxicity, but there is no evidence of benefit.
- For women with previous history of thrombosis. Since warfarin is contraindicated during the first trimester of pregnancy, we switch to aspirin plus subcutaneous LMWH (dalteparin) at a dose of 5000 U daily. The dose is doubled in the 16th to 20th weeks. We no longer routinely determine anti-Xa levels. Patients with previous stroke may present with neurological symptoms during pregnancy despite maximal doses of dalteparin (5,000 U twice a day). In these cases warfarin is re-introduced in the second trimester, with a target INR of 2.5. Close monitoring of anticoagulation is needed.
- For women with a history of first trimester pregnancy losses, we treat with aspirin alone. Adding heparin during at least the first 13 weeks may be appropriate [53].
- For women with a history of fetal death, we add subcutaneous dalteparin at a dose of 5,000 U daily throughout the pregnancy without monitoring anti-Xa levels.
- For women with a previous miscarriage on aspirin, we offer dalteparin 5,000 U daily throughout the next pregnancy.
- All patients treated with heparin receive aspirin as well, unless contraindicated for some reason.
- In women receiving dalteparin for thromboprophylaxis (i.e., with previous history of thrombosis), the drug is omitted once they are in established labor, followed by 5,000 U once the placenta has been delivered. Heparin is continued on a twice-a-day basis for 3 days and then continued at 5,000 U daily until warfarin is re-started.
- Calcium 1,000 mg/day, plus vitamin D3 400 IU/day, are given to every woman treated with heparin.
- Treatment with immunoglobulins or even low dose prednisolone may be considered for women with persistent pregnancy losses despite full treatment with aspirin and heparin. These approaches are mostly experimental.

Congenital lupus
Cutaneous involvement is usually benign and transient, and nothing other than sun protection or topical low potency steroids is usually needed [37]. In cases with demonstrated congenital heart block, established third-degree
block is not treated in utero unless accompanied by effusions (pleural, pericardial or ascites), signs of congestive heart failure or hydrops. If any of the latter occurs, or if there is evidence of a recent complete or incomplete (first or second-degree) heart block, treatment is established with dexamethasone 4 mg daily. If there is no response after several weeks it is stopped [37].

Conclusions

Pregnancy is high risk in women with SLE and APS. Mothers with lupus are likely to flare, though most flares are not severe. Patients with APS are at increased risk of thrombosis and preeclampsia. The fetus can be affected by maternal SLE activity — especially renal disease — and hypertension, and by the presence of aPL, anti-Ro and anti-La.

Management of these pregnancies includes closer obstetric surveillance, prompt recognition of maternal SLE flares and therapy according to their severity, thomboprophylaxis with LMWH and treatment with aspirin in women with APS, and monitoring for heart block in babies of mothers anti-Ro and/or anti-La positive. If adequately managed, most pregnancies in women with SLE and APS are nowadays successful.

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References

53. Bone morphogenetic protein-Z, a growth factor produced by bone cells. These results raise the possibility that with optimization of dose and tissue distribution properties, the statins may have beneficial effects in the prevention and treatment of osteoporosis.

**Boning up on statins**

Nearly 100 million people worldwide are at risk for osteoporosis, a debilitating disease of bone loss, and this number is expected to rise as the population ages. Mundy et al. show that the statins, a group of drugs commonly prescribed to lower serum cholesterol levels, also stimulate bone formation in vitro and in rodent models. This effect was associated with increased expression of bone morphogenetic protein-Z, a growth factor produced by bone cells. These results raise the possibility that with optimization of dose and tissue distribution properties, the statins may have beneficial effects in the prevention and treatment of osteoporosis.

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