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Pregnancy outcome in systemic lupus erythematosus complicated by anti-phospholipid antibodies

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Objective. Pregnant women affected by SLE are at high risk of gestational hypertension and pre-eclampsia (32–50%). This risk is particularly elevated if aPLs are dosable. The present study was planned to evaluate maternal–fetal outcomes of different groups of SLE pregnant patients characterized by diverse risk factors: patients affected by APS treated with a combination of low-dose aspirin (LDA) and low-molecular weight heparin (LMWH), nulliparous patients with dosable aPL treated by LMWH and SLE patients with no aPL administered no treatment during pregnancy.
Methods. A retrospective description of maternal and fetal outcomes was made in a total of 62 pregnancies presenting APS in 8 cases (12.9%), aPL in 20 (32.2%) and no aPL in 34 (54.8%).
Results. No statistically significant difference was found comparing fetal and maternal outcomes of the three groups despite differences in SLE activity: SLE aPL-positive pregnancies were associated with a higher incidence of nephritis and chronic hypertension than pregnancies treated for APS or not presenting with the added risk factor. The incidence of pre-eclampsia is 15% in aPL positive, 12.5% in APS and 14.7% in no aPL pregnancies, respectively.
Conclusions. LMWH is rather a possible option of prophylaxis for SLE aPL-positive pregnancies with potential maternal–fetal outcomes similar to aPL-negative patients or to standard treated APS.

Key words: Systemic lupus erythematosus, Activity, Anti-phospholipid antibodies, Anti-phospholipid syndrome, Pregnancy, Pregnancy outcome, Gestational hypertension, Pre-eclampsia, Low molecular weight, Heparin.

Introduction

SLE is a systemic inflammatory disease of unknown aetiology with a polymorphic clinical picture characterized by the presence of autoantibodies against a large number of tissue components, principally directed towards cellular nucleus antigens.

SLE is prevalent in women with an incidence peak in childbearing age. In SLE, no known fertility reduction is reported except for patients with severe renal insufficiency, or premature ovarian failure produced by immunosuppressive drugs, such as cyclophosphamide [1]. Some studies, addressing the problem if and how pregnancy may affect the disease, have led to controversial conclusions, in particular concerning the incidence of flare and organ involvement [1–4]. On the other hand, SLE effects on the course of pregnancy are well documented in literature. In fact, despite that the advances in medical, obstetric and neonatal management have slightly improved pregnancy outcome, SLE still remains associated with significant maternal and fetal morbidity, like spontaneous miscarriage, pre-eclampsia, intrauterine growth restriction (IUGR), fetal death and pre-term delivery [2].

Many studies have attempted to define the pathogenetic process responsible for the perinatal outcome in SLE pregnant patients. The following factors have been found of relevance: disease activity at the time of conception, presence of lupus nephritis, of aPLs, of anti-SSA/Ro or anti-SSB/La antibodies and pre-pregnancy maternal hypertension [3]. Nevertheless, the pathogenetic mechanism remains unknown.

Above all, the role of aPLs, reported in 30–80% of the affected patients, seems to be particularly important, since they could be responsible for both maternal thromboembolic disease and placental insufficiency with pre-term labour, IUGR, pre-eclampsia and eventually fetal death [4–7].

In the majority of previous studies, SLE pregnant patients with aPL were untreated while patients with APS only were treated [5]. Moreover, most studies were retrospective involving small groups of SLE pregnant women with APS, recruited over a large time span and receiving different treatments (steroids, heparin, aspirin) [5, 8].

We conducted a retrospective study to evaluate maternal and fetal outcomes in three groups of SLE pregnant patients: one group of primigravid patients positive to aPLs treated with low-molecular weight heparin (LMWH) prophylaxis, a second of patients affected by APS and treated with LMWH and low-dose aspirin (LDA), and a third one without aPLs and no treatment.

Materials and methods

The study included 58 patients with SLE (for a total of 62 pregnancies) referred to the High-risk Pregnancy Unit of the Department of Gynaecology, University of Florence, between January 1998 and June 2006.

All patients were seen in the pre-conceptional phase, and met at least four of the revised criteria for SLE [9]. In this phase, all patients were advised to plan pregnancy after at least 6 months of low disease activity.

At baseline, patients' medical, clinical and laboratory history was taken together with maternal informations, including personal data, obstetric antecedents, duration of SLE, previous and current SLE manifestations and previous therapy.

During pregnancy patients were seen every 4 weeks until the 27th week and on a weekly basis thereafter, until delivery. In the post-partum period the patients were seen monthly for 3 months.

Baseline laboratory data included an initial assessment (followed by monthly control tests) consisting of: complete blood count, serum creatinine, protein, albumin, glucose and uric acid, urinalysis and 24-h urine protein excretion. The initial immunological evaluation included the determination of LAC, aCLs and a panel of autoantibodies (anti-B2-glycoprotein I, anti-Ro/SSA, La/SSB and anti-SM). Every trimester the following

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immunological tests were evaluated: C3, C4, CH50, direct and indirect Coombs test, anti-dsDNA and ANA.

LAC and aCLs (IgG and IgM) were obtained from all patients prior to conception. LAC screening was performed by coagulation assays using a LAC-sensitive activated partial thromboplastin time (aPTT), dilute Russell's viper venom time (dRVVT) and kaolin clotting time (KCT). LAC presence was confirmed by the correction of the extended clotting time with high concentration of phospholipids. The aCLs were measured by a commercially available ELISA (First Cardiolipina, Eurospital, Trieste, Italy). Patients were considered to have aPL if LAC or aCLs were present in two or more occasions at least 6 weeks apart, as defined by the international consensus statement [10]. The aCLs were considered to be positive if there were moderate or high levels of IgG and/or IgM (>20 GPL or MPL units).

Flare activity was scored before and after pregnancy with the SLEDAI [11]. Flare was defined as every clinical manifestation of activity with or without new onset or worsening of leukopenia, thrombocytopenia, Coombs positive haemolytic anaemia, proteinuria and an increased serum level of anti-dsDNA antibodies or a decreased level of serum C3 and C4.

Regarding the fetal examination, routine ultrasound scans were performed (in the first trimester for dating the pregnancy, in the second trimester for the fetal anatomy). From the 22nd week the pregnancy was monitored by further ultrasound scans to control blood flow velocimetry of uterine arteries (22–24 weeks), umbilical arteries (every month) and fetal growth (every month); fetal echocardiography was performed in all cases at 17–18 weeks' gestation, and then repeated at 24 and 30 weeks in patients with anti-SSA and/or anti-SSB antibodies. From 36 weeks onwards, a cardiotocography (CTG) was performed on a weekly basis. In case of IUGR, APS, flare, hypertension or worsening of renal functionality, CTG tracings were started earlier as appropriate.

The patients with APS received, after confirming the pregnancy with a urine pregnancy test (levels of HCG >50 IU/ml), LDA (100 mg/day) and LMWH (dalteparin 5000 IU/day s.c.), upon visualization of embryonic cardiac activity (at 5–6 weeks' gestation) using conventional transvaginal ultrasound. Aspirin was under normal circumstances suspended at 34, or earlier in case of miscarriage or onset of pre-term labour.

Nulliparous patients with aPL received LMWH (dalteparin 5000 IU/day s.c.), upon visualization of embryonic cardiac activity (at 5–6 weeks' gestation) using conventional transvaginal ultrasound. The group of patients negative for aPL were not treated.

All studied patients were treated until the conception period with low dose prednisone (5 mg/day) and during flare the dose of prednisone was increased according to the patient's weight.

All patients were supplemented with iron and vitamins; calcium carbonate (1.5 g/day) was prescribed in women receiving LMWH.

Negative maternal outcome was considered as one or more of the following events: miscarriage (spontaneous loss before 10 weeks' gestation), pre-eclampsia (systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg associated with proteinuria >300 mg/24 h), lupus flare, and therapeutic termination of pregnancy because of flare.

The following parameters of perinatal outcome for live births were considered: pre-term labour (live birth before 37 weeks' gestation), IUGR (birth weight <10th percentile of the standard growth curve), birth weight, Apgar index at 1 and 5 min and neonatal ponderal index (PI, defined as the ratio between weight in grams and height in centimetres × 100), which is a gestation- and gender-independent dimensionless variable, which reflects the greater impact of protein-calorie malnutrition (intrauterine growth restriction) on muscle and fat mass when compared with skeletal growth [12]. Newborns with a PI <2.32 may be considered nutritionally deprived [13].

TABLE 1. Demographic and clinical characteristics of the patients

Patients	aPL+ ($n=20$)	APS ($n=7$)	aPL− ($n=31$)	P
Maternal age, mean ± S.D., yrs	36.6 ± 4.10	37.12 ± 3.18	34.5 ± 5.57	NS
SLE length, mean ± S.D., yrs	6.2 ± 5.61	6.5 ± 4.23	6.0 ± 5.83	NS
LAC, *n* (%)	14 (63.6)	5	0	-
ACA, *n* (%)	11 (50)	3	0	-
SSA/SSB, *n* (%)	7 (31.8)	2	7 (29.1)	NS
SLE active, *n* (%)	5 (25)	1(14.2)	2 (6.4)	NS
Prior lupus nephritis, *n* (%)	7 (35)	3 (42.8)	4 (12.9)	NS
Chronic hypertension, *n* (%)	7 (35)	2 (28.5)	4 (12.9)	0.03
Pregnancies, *n*	20	8	34	NS

Statistical analysis

The quantitative variables have been estimated with the Student's *t*-test, while the qualitative variables have been calculated with the χ^2-test. A *P*-value of <0.05 was considered statistically significant.

Results

The demographic characteristics of the three groups are shown in Table 1. Out of 58 patients (62 pregnancies) enrolled in the study, 20 (34.4%) were aPL positive (three women were positive for both antibodies) and 7 (12%) had APS. In the aPL group, all patients were nulliparous. None of the aPL and APS patients developed thromboembolic events. The mean age was similar in the three groups. At the first pre-conceptional examination, maternal SLE was active in 25% of aPL group, in 14.2% of APS and 6.4% in aPL-negative group. In aPL-positive patients and in APS, an increased number of patients with previous lupus nephritis and chronic hypertension with respect to aPL-negative patients, was detected ($P < 0.03$) At pregnancy onset, 10 aPL-positive patients, 3 APS patients and 13 aPL-negative patients were on steroids with an average prednisone dosage of 7.8 mg/day (range 5–20).

Maternal outcome

In the observed 62 pregnancies, there were three (15%) miscarriages in aPL patients, two in APS (28.5%) and six (17.6%) in no aPL patients (equally distributed in the two study groups) and one ectopic pregnancy. Fifty-one pregnancies (82.2%) continued beyond the first trimester.

Overall, 16 episodes of flare were observed: eight in the aPL-positive group, one in the APS and seven in aPL-negative group. Regarding SLE flare, it was mild to moderate in 56.2% (9/16) of the cases, with manifestations that did not require modification of the therapy. Severe flare occurred in 43.7% (7/16) of the pregnancies and was mainly characterized by nephritis.

In the group of 51 pregnancies that continued beyond the first trimester, nine (9/51, 17.6%) have been complicated by pre-eclampsia: 15% in aPL, 12.5% in APS and 14.7% in aPL negative. Two of these patients developed haemolytic anemia, elevated liver enzymes and low platelet count (HELLP) syndrome, one in the aPL and one in APS group.

Fetal outcome

In our study population of 62 pregnancies, we had 51 deliveries (82.2%): 85% (17/20) in the aPL positive and 75% (6/8) in the APS and 82.3% (28/34) in aPL negative. There were 11 miscarriages before 10 weeks' gestation. The pre-term delivery rate was 29.4% (15 out of 51); 3 patients among aPL negative, were pre-term delivery <34 weeks (Table 2).

There were no cases of neonatal lupus or congenital heart block. Regarding birth weight, PI and the number of the neonates with a birth weight less than 10th percentile (IUGR), there was no statistically significant difference between the two groups. The IUGR rate was 19.6% (10/51).

TABLE 2. Fetal outcome

Outcome	aPL ($n=20$)	APS($n=8$)	No aPL($n=34$)	P
Live births $N=51$, n (%)	17 (85)	6 (75)	28 (82.3)	NS
Gestational age at delivery, mean ± S.D., weeks	38.04 ± 1.96	36.5 ± 1.8	38.03 ± 2.8	NS
Pre-term labour n (%)	5 (25)	2 (37.5)	8 (23.5)	NS
Birth weight, mean ± S.D.	2780 ± 520.27	2435 ± 621.4	2893 ± 655.61	NS
PI, mean ± S.D.	2.46 ± 0.44	2.78 ± 0.05	2.60 ± 0.29	NS
Neonatal weight <5° n (%)	3 (20)	1 (12.5)	5 (14.7)	NS

NS: not significant.

Discussion

In SLE patients, the presence of aPLs is one of the risk factors heralding complications and flare during pregnancy. The aPLs, found in 30–80% of affected patients, have a role in the pathogenesis of both maternal thromboembolic disease and placental insufficiency with consequent pre-term labour, IUGR, pre-eclampsia and ultimately fetal death [4–6].

Different therapeutic regimens (corticosteroids, aspirin, heparin or a combination of them) have been evaluated in long-term studies to improve fetal and maternal outcomes of aPL patients [14–17], reaching a widespread agreement on the benefit of anti-thrombotic prophylaxis.

Combined therapy with LWMH and LDA is considered as the standard treatment for APS patients to reduce the incidence of recurrent miscarriage, intrauterine growth restriction, pre-eclampsia, HELLP syndrome and fetal death [18].

Thus, while previous thromboembolic events and negative obstetric antecedents constitute a sufficient basis for prophylaxis, there is no consensus on the fact that an anti-thrombotic procedure may have a benefit in asymptomatic aPL-positive patients in their first pregnancy [19].

Khamashta *et al*. [18] suggested that a prophylaxis exploiting the anti-coagulant effect of LDA might play a fundamental role in protecting pregnancies of aPL-positive but not symptomatic nulliparous patients, influencing the prevalence of placental accelerated atherosclerosis of these patients.

Recently, the involvement of endothelial dysfunction in the pathogenesis of cardiovascular disease, hypertension and placental dysfunction during pregnancy has been recognized. Comparing factors of vascular function between normal and SLE patients, a significant reduction of the endothelial-mediated vasodilation, index of precocious atherosclerosis in SLE patients, was detected [20].

Up to date, there is a level of evidence evaluated as 9 in a scale from 0 to 10 by the Task Force of the EULAR Standing Committee for International Clinical Studies that LDA should be used in adult SLE patients receiving corticosteroids, in those with dosable aPL and in those with at least one traditional risk factor for atherosclerotic disease, as primary prevention of thrombosis and all the other manifestations of APS including abortion or fetal loss [21].

Girardi *et al*. [22] in an experimental *in vivo* study recently demonstrated that anti-coagulant effect can be considered necessary but not sufficient in protecting aPL-induced fetal losses. She suggested that complement system activation, especially C3 and C5, is an important mechanism of anti-phospholipid-induced pregnancy loss. C3 and C5 activation is supposed to amplify pro-coagulant effects of aPL. Heparin seemed to prevent aPL-induced pregnancy loss by inhibiting C3 and C5 activation rather than its anti-coagulant effect [22].

Our experience shows that the use of LWMH in the treatment of asymptomatic aPL-positive nulliparous pregnancies brings their incidence of fetal complications to be similar to the one presented by standardly treated APS patients and moreover to those patients who are aPL negative.

Moreover, the present case series shows that LMWH may primarily prevent maternal complications, such as pre-eclampsia, reducing its incidence to that presented by SLE pregnant aPL-negative patients even when related risk factors are present as a higher incidence of chronic hypertension and lupus nephritis.

This result is in agreement with previuos data that described LMWH as protective for recurrent pre-eclampsia in non-SLE pregnant patients [23].

In our work, LMWH was preferred to unfractioned heparin (UFH) mainly because of its usefulness described in literature. In a randomized pilot trial study, in pregnancy comparing LMWH, specifically dalteparin, to UFH for the treatment of APS, found higher successful pregnancy rate in the dalteparin group (69%) (95% CI 39%, 91%), than in the UFH group (31%) (95% CI 9%, 61%) [24].

In conclusion, although the present study is limited by its retrospective methodology, LMWH prophylaxis seems rather to be a possible option for first pregnancy of SLE aPL-positive patients who may reach maternal–fetal outcomes similar to aPL-negative patients or to standard treated APS.

A prospective randomized study comparing outcomes of aPL-positive pregnancies treated with LMWH and untreated aPL-positive pregnancies is currently ongoing to better clarify if LMWH might be in future considered as a tool for primary prevention of uneventful aPL-induced outcomes of SLE pregnant women.

Rheumatology key messages

- aPLs are an added risk factor for negative maternal–fetal outcomes in SLE pregnant patients.
- LMWH in SLE patients at their first pregnancy is an option of prophylaxis to protect them from negative maternal–fetal outcomes.

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