Rheumatology 2008;47:646–651
Advance Access publication 17 March 2008
doi:10.1093/rheumatology/ken046

Intravenous immunoglobulin therapy in pregnant patients affected with systemic lupus erythematosus and recurrent spontaneous abortion

R. Perricone[1], C. De Carolis[2], B. Kröegler[1], E. Greco[1], R. Giacomelli[3], P. Cipriani[3], L. Fontana[4] and C. Perricone[1]

Objectives. We aimed to test the maternal and fetal outcome of SLE patients who suffered from recurrent spontaneous abortion (RSA) treated with intravenous immunoglobulin (IVIg) alone during pregnancy and whether the clinical response to IVIg treatment is accompanied by modifications of SLE-associated antibodies and of complement levels.
Methods. Twelve SLE-RSA pregnant patients were treated with high-dose IVIg and compared with 12 SLE-RSA pregnant patients treated with prednisolone and NSAIDs. They were evaluated for the clinical response [lupus activity index-pregnancy (LAI-P) scale] and for ANA, anti-dsDNA, anti Ro/SS-A or La/SS-B, aCL, LAC, C4, C3 before and during pregnancy, and before and after each treatment course. Pregnancy outcome in the two groups was also evaluated.
Results. The groups characteristics were homogeneous at the beginning of pregnancy. A beneficial clinical response following IVIg treatment was noted in all patients and mean LAI-P decreased from 0.72 ± 0.43 at the beginning of pregnancy to 0.13 ± 0.19 at the end of pregnancy ($P < 0.0001$). Antibodies and complement levels tended to normalize in most of the patients. These clinical and laboratory improvements were significant with respect to the control group. Pregnancy was successfully carried out in 12/12 (100%) SLE-RSA patients with a mean Apgar score of 8.92. Three patients in the control group got aborted (25%).
Conclusions. IVIg has a high response rate among SLE-RSA pregnant patients and may be considered safe and effective.

Key words: SLE, IVIg, APS, Pregnancy.

Introduction

SLE is the autoimmune disease that most commonly jeopardizes pregnancy. Indeed, in most studies, when analysing the relationship between SLE and pregnancy, it is reported that an increase of fetal and maternal risks notably when pregnancy occurs in active SLE [1].

Potential adverse events consist of miscarriage, premature delivery, intrauterine fetal growth restriction and flares of lupus activity, which can range from mild clinical findings to a life-threatening condition. The most important predictors of poor obstetric outcome are lupus activity and the presence of aPLs that, together with suggestive clinical features, may result in the APS. Maternal morbidity may be severe during an SLE exacerbation and treatment itself is limited by pregnancy: nonetheless, active SLE places the embryo, fetus and the neonate at enormous risk [2]. Recurrent spontaneous abortion (RSA), defined as the presence of three or more previous consecutive pregnancy losses, is not uncommon in SLE patients. When treating a patient with SLE, the aim is to suppress the disease activity and to prevent the onset of organ damage. Clearly, dilemmas arise in pregnant lupus patients regarding appropriate treatment to control active disease, weighting the potential benefits against risks [3].

Many treatments have been proposed so far, but therapy of SLE in pregnancy still remains empirical and not evidence based, generally not risk-free and adapted to each patient situation [4–6].

Intravenous immunoglobulin (IVIg) therapy is now approved in several autoimmune diseases, and in all cases in which pathogenic auto-antibodies or immune complexes are thought to be directly involved [7–10]. Moreover, it has also been used in recurrent miscarriage and infertility [11–13]. In recent years, many reports of the use of IVIg in SLE have been gathered. The largest study with SLE non-pregnant patients (20 patients) demonstrated an 85% response rate [14] and in several small case series involving 3–12 patients the general efficacy ranged between 33% and 100%. As the treatment of SLE often includes immunosuppressive drugs, IVIg offers, in addition to immunomodulatory properties, protection from infections in immunosuppressed patients.

No previous reports of patients with SLE and RSA treated with IVIg during pregnancy have been described so far. Taking into account the potential of IVIg, the effectiveness of this therapy in patients with SLE and in antiphospholipid-associated obstetric complications, the good results reported in the literature, the unsatisfactory response of our patients to other treatments in previous pregnancies and finally considering our experience with SLE, IVIg and pregnancy, we used IVIg in SLE pregnancy.

The aim of the study was to evaluate the efficacy of IVIg treatment on maternal and fetal outcome in pregnant patients affected with SLE who suffered from RSA. For this purpose, we selected a control age- and ethnicity-matched group composed of pregnant patients affected with SLE and RSA treated by means of standard therapy during pregnancy.

Patients and methods

Subjects

Twelve Caucasian Italian patients affected by SLE and RSA who were referred to the Department of Gynaecology and Obstetrics, S. Giacomo Hospital, ASL RMA, Rome, Italy and/or to the Center for the Prevention, Diagnosis and Therapy of Recurrent Spontaneous Abortion, ASL RMC, Rome, Italy were evaluated.

This population was composed of eight patients affected only with SLE and RSA and four with SLE and APS due to the presence of aPL and RSA. SLE and APS diagnoses were made in accordance with international guidelines (all patients fulfilled ACR revised criteria for SLE and Sapporo's clinical and

[1]Department of Rheumatology, University of Rome Tor Vergata, [2]S. Giacomo Hospital, ASL RMA, Gynaecology and Obstetrics, [3]Department of Rheumatology, University of L'Aquila, L'Aquila and [4]Department of Internal Medicine, University of Rome Tor Vergata, Rome, Italy.

Submitted 3 July 2007; revised version accepted 21 January 2008.

Correspondence to: R. Perricone, Chief of Rheumatology Policlinico Tor Vergata Hospital, Chair of Allergology, Clinical Immunology and Rheumatology, Department of Internal Medicine, University of Rome Tor Vergata, Via Montpellier 1, 00133 Rome, Italy. E-mail: roberto.perricone@uniroma2.it

laboratory criteria and the revised criteria for APS diagnosis) [15–17]. None of the patients reported herein showed any infectious or parasitic disease. Mean age of the patients was 34.67 ± 4.27 yrs (Table 1).

All patients presented in their clinical history RSA, defined as three or more previous consecutive pregnancy losses (mean 3.5 ± 0.67). Study protocol was performed in all patients and included clinical and abortive anamnesis, gynaecological exams, karyotype study, serum creatinine, protein, albumin, glucose, urine analysis, autoantibodies screening including ANA, anti-ENA, anti-mitochondrial antibodies, ASMA, anti-thyroperoxidase and thyroglobulin antibodies, ANCA and aPL dosage, coagulation assays, endocrine evaluation, thyroid functionality evaluation, including thyroid echography, hysteroscopy and pelvic echography, colposcopy, thrombophilic evaluations and cultural assays for the research of common germs, *Mycoplasma* spp. and *Chlamydiae* spp.

For a relevant control group we selected 12 women with similar demographic features affected with SLE and RSA diagnosed as previously reported (mean age 34.92 ± 3.53 yrs, Table 1). This group underwent the same study protocol.

Disease activity was scored at the beginning of pregnancy, before initiating the IVIg treatment and at any IVIg course by means of the lupus activity index-pregnancy scale (LAI-P; range 0–2.6) [18, 19]. Disease activity in the control group was scored at the same time courses. Clinical manifestations and laboratory findings were, when LAI-P score was performed, evaluated for amelioration/worsening of the parameter according to LAI-P scale, otherwise were scored for presence or absence. Gestational age at delivery was determined by menstrual dates, confirmed by ultrasound examination. Written informed consents of all the patients were obtained according to the Declaration of Helsinki. The design of the study conforms to standards currently applied in Italy (DR 23.07.1993, no. 4218; DLgs. 13.02.1993, no. 40).

Therapeutic regimen before and during pregnancy

In the IVIg-group, before pregnancy, two patients assumed prednisolone 0.25–0.5 mg/kg, one >0.5 mg/kg and one <0.25 mg/kg. Nine patients assumed NSAIDs. Treatment with prednisolone and NSAIDs was discontinued as IVIg therapy was initiated.

As soon as pregnancy was confirmed by a positive serum βHCG titre and by the presence of a gestational sac detected by ultrasound, IVIg (Flebogamma®; Grifols, Pisa, Italy) treatment was initiated and carried out at the Department of Internal Medicine of the University of Rome Tor Vergata in all the 12 patients.

The treatment protocol was as follows: 0.5 g IVIg/kg body weight were infused once every 3 weeks over a 6-h infusion (2 ml/min). Treatment ended at the 33rd week of pregnancy [13].

All the patients remained in the hospital during the day of infusion and were discharged in the evening as no adverse reactions were observed.

In the control group, before pregnancy, nine patients assumed prednisolone 0.25–0.5 mg/kg and three <0.25 mg/kg. All patients but one assumed NSAIDs. One patient also assumed AZA (1 mg/kg). As soon as pregnancy was confirmed as reported above, therapeutic regimen protocol was prednisolone 0.25–0.5 mg/kg and aspirin (100 mg daily). Treatment with aspirin and prednisolone was discontinued at the 34th gestational week or at the time of miscarriage. AZA was discontinued at the beginning of pregnancy, but it was reintroduced later due to SLE flares.

Laboratory evaluation

All tests were carried out at the beginning of pregnancy, during pregnancy and at the end of pregnancy. Tests were repeated at least 12 weeks apart.

ANA quantification was performed by DIFA and a positive level was considered ≥1:80. Anti-dsDNA antibodies were detected in a fluorescence assay with the kinetoplast of *Crithidia luciliae*. ENA were measured by means of a standard ELISA considering a cut-off value > 20 UI.

Patients were screened for the presence of aPL (aCL and β_2GP-I IgM and IgG class) according to international guidelines using previously described methods through ELISA assays [15, 16, 20]. Tests were considered positive when aCL of the IgG and/or IgM isotype at a medium or high titre (>40), and/or anti-β_2GP-I antibodies of IgG and/or IgM isotype in titre >99th percentile were present in blood on two or more occasions at least 12 weeks apart. LAC was detected by coagulation assays adhering to the International Society of Thrombosis and Haemostasis [21]. Complement factors (C3 and C4) were measured in accordance with the international guidelines [22]. C4 normal range was considered 10–40 mg/dl and C3 normal range was 90–180 mg/dl.

Most of the subjects who entered this study had not been followed by our group during previous pregnancies. Only patients who underwent the complete screening, who were not using any other treatment but the aforementioned and who had never previously been treated by means of IVIg were admitted.

TABLE 1. Outcome of the 12 SLE-RSA pregnant patients treated with IVIg compared with the control group

IVIg-treated group (A) *vs* non-IVIg-treated group (B)											
Delivery status		Week of pregnancy		Weight (kg)		Apgar score (top score 10)		Age (years)		No. of previous abortions	
A	B	A	B	A	B	A	B	A	B	A	B
CS	CS	38	38	3.80	3.35	9	8	35	30	3	3
CS	CS	38	36	4.20	2.95	9	9	37	39	3	3
CS	SD	38	33	3.20	3.45	9	9	32	32	3	3
CS	SA	38	7[a]	4.02	NA	9	NA	40	35	3	3
CS	SA	38	11[a]	3.50	NA	9	NA	34	34	3	3
CS	CS	36	42	2.93	4.26	10	9	39	37	3	3
CS	SD	38	37	3.30	2.89	8	9	36	41	3	3
CS	CS	36	39	2.20	2.80	10	8	23	33	4	3
CS	SD	38	36	3.40	3.15	9	8	34	31	4	3
CS	CS	36	36	2.20	2.75	8	7	35	36	4	3
SD	CS	38	38	2.90	3.40	9	8	35	39	4	4
CS	SA	38	23[a]	3.60	NA	8	NA	36	32	5	6
Mean		37.50	37.22	3.27	3.22	8.92	8.33	34.67	34.92	3.50	3.33
S.D.		0.90	2.49	0.63	0.47	0.67	0.71	4.27	3.53	0.67	0.89

CS, Caesarean section; SD, Spontaneous delivery; SA, Spontaneous abortion; NA, not applicable. [a]Week of abortion.

Statistical analysis

The statistical analysis was performed by means of a computer-assisted statistical analysis program (GraphPad Prism 5.0). Comparisons between the groups were performed with the two-tailed Student's *t*-test (*P*-values). Analysis of the effects of IVIg, prednisolone and aspirin, pregnancy, patients response and interaction of both factors as grouping variables was performed by two-way analysis of variance (ANOVA).

When more than two groups were simultaneously considered, inter-group differences were analysed by one-way ANOVA corrected with Bonferroni's multiple comparison test (P_c-values).

Two-tailed *P*-values were reported together with 95% CI of differences, and *P*-values <0.05 were reported to be statistically significant.

Results

Effects of IVIg on pregnancy, live birth rate and maternal outcome

Pregnancy outcome was successful in all patients treated by means of IVIg, despite the history of RSA. Mean pregnancy duration was 37.5 ± 0.9 weeks (36–38). Caesarean section was carried out in 11 (91.7%) patients, while 1 (8.3%) had spontaneous delivery at the 38th week of gestation. Full-term birth occurred in nine (75%) cases, whereas pre-term delivery (36th week) occurred in three (25%). Average neonatal birth weight was 3270 ± 630 g (2200–4200) and mean Apgar score was 8.92 (Table 1). No diseases were observed in the newborns.

In the control group, only 9 patients upon 12 successfully delivered (75%), while the other 3 had spontaneous abortion, respectively at the 7th, 11th and 23rd gestational week. Considering successful deliveries, mean pregnancy duration was 37.22 ± 2.49 weeks (33–42). Caesarean section was carried out in six (66.7%) patients, while three (33.3%) had spontaneous delivery. Full-term birth occurred in four (44.4%) cases, whereas pre-term delivery occurred in five (55.6%). Average neonatal birth weight was 3222 ± 470 g (2750–4260) and mean Apgar score was 8.33 (Table 1). No diseases were observed in the newborns. Table 1 describes patients features.

Effects of IVIg on clinical manifestations

Table 2 shows the presence of individual disease clinical manifestations before and after IVIg therapy (i.e. at the beginning and at the end of pregnancy) in the IVIg-treated group. After IVIg therapy, these manifestations were absent (out of the total number of patients with the presence of manifestations): 9/10 (90%) patients with arthritis, 6/7 (85.7%) with fever, 2/2 (100%) patients with malar rash, 2/2 (100%) with serositis, 5/6 (83.3%) with haematological involvement (leucopoenia), 3/6 (50%) with haematological involvement (thrombocytopenia), 1/1 (100%) with neurological involvement (seizure), 1/1 (100%) with myositis, 5/6 (83.3%) with haematuria and presence of urinary sediment (blood casts) and 1/1 (100%) with proteinuria. No patients presented lung involvement or vasculitis, nor SLE flares.

Control group demonstrated similar clinical features before pregnancy. During pregnancy, patients did not have such a dramatic clinical improvement. Nonetheless, one patient had SLE flares requiring immunosuppressive drug (AZA) to control the flares. Table 3 shows the individual disease clinical manifestations at the beginning and at the end of pregnancy in the control group.

Effects of IVIg on autoantibodies and complement levels

Table 4 shows the presence of individual abnormal levels of autoantibodies and complement before and after IVIg therapy in the IVIg-group. After IVIg therapy, autoantibodies and complement levels turned into normal (out of the total number of patients with abnormal levels): anti ds-DNA 6/6 (100%), ANA 9/12 (75%) anti Ro/SS-A 1/3 (33.3%), anti La/SS-B 3/3 (100%), aCL IgG 2/4 (50%), aCL IgM 2/2 (100%), low C4 4/5 (80%) and low C3 5/5 (100%). Only LAC remained unchanged.

A mild improvement in laboratory exams was observed in the control group; however, few patients had a worsening in some of these assays. Data are shown in Table 5.

Effects of IVIg on disease activity

Figure 1 shows each patient's mean LAI-P at the beginning of pregnancy, when IVIg treatment was initiated, and at the end of pregnancy, when IVIg treatment was discontinued. In the

Table 2. Clinical features of the 12 SLE-RSA pregnant patients treated with IVIg before IVIg therapy, at the beginning of pregnancy and after IVIg therapy, at the end of pregnancy

	Number of patients with the presence of clinical manifestation(s)	
Clinical manifestation	Beginning of pregnancy (%)	End of pregnancy (%)
Arthritis	10 (83)	1 (8.3)
Fever	7 (58.3)	1 (8.3)
Malar rash	2 (16.7)	0
Serositis	2 (16.7)	0
Haematological involvement (thrombocytopenia)	6 (50)	3 (25)
Haematological involvement (leucopoenia)	6 (50)	1 (8.3)
Neurological involvement (seizures)	1 (8.3)	0
Myositis	1 (8.3)	0
Renal involvement (haematuria—blood casts)	6 (50)	1 (8.3)
Renal involvement (proteinuria)	1 (8.3)	0

Table 3. Clinical features of the control group

	Number of patients with the presence of clinical manifestation(s)	
Clinical manifestation	Beginning of pregnancy (%)	End of pregnancy (%)
Arthritis	7 (58.3)	1 (8.3)
Fever	7 (58.3)	1 (8.3)
Malar rash	6 (50)	4 (33.3)
Serositis	3 (25)	1 (8.3)
Haematological involvement (thrombocytopenia)	6 (50)	3 (25)
Haematological involvement (leucopoenia)	6 (50)	1 (8.3)
Renal involvement (haematuria—blood casts)	3 (25)	1 (8.3)
Renal involvement (proteinuria)	4 (33.3)	2 (16.7)

The patients were evaluated at the beginning of pregnancy and at the end of pregnancy.

Table 4. Main laboratory parameters of the 12 SLE-RSA pregnant patients treated with IVIg before IVIg therapy, at the beginning of pregnancy and after IVIg therapy, at the end of pregnancy

	Number of patients	
Antibody	Beginning of pregnancy (%)	End of pregnancy (%)
Anti ds-DNA	6 (50)	0
ANA (homogeneous)	7 (58.3)	2 (16.7)
ANA (speckled)	5 (41.7)	1 (8.3)
Anti Ro/SS-A	3 (25)	2 (16.7)
Anti La/SS-B	3 (25)	0
aCL IgG	4 (33.3)	2 (16.7)
aCL IgM	2 (16.7)	0
LAC	4 (33.3)	4 (33.3)
Complement profile		
C4	5 (41.7)	1 (8.3)
C3	5 (41.7)	0

TABLE 5. Main laboratory parameters of the control group

	Number of patients	
	Beginning of pregnancy (%)	End of pregnancy (%)
Antibody		
Anti ds-DNA	12 (100)	9 (75)
ANA (homogeneous)	5 (41.7)	4 (33.3)
ANA (speckled)	7 (58.3)	5 (41.7)
Anti Ro/SS-A	3 (25)	1 (8.3)
Anti La/SS-B	1 (8.3)	0
aCL IgG	4 (33.3)	1 (8.3)
aCL IgM	1 (8.3)	0
LAC	5 (41.7)	2 (16.7)
Complement profile		
C4	6 (50)	2 (16.7)
C3	5 (41.7)	3 (25)

The patients were evaluated at the beginning of pregnancy and at the end of pregnancy.

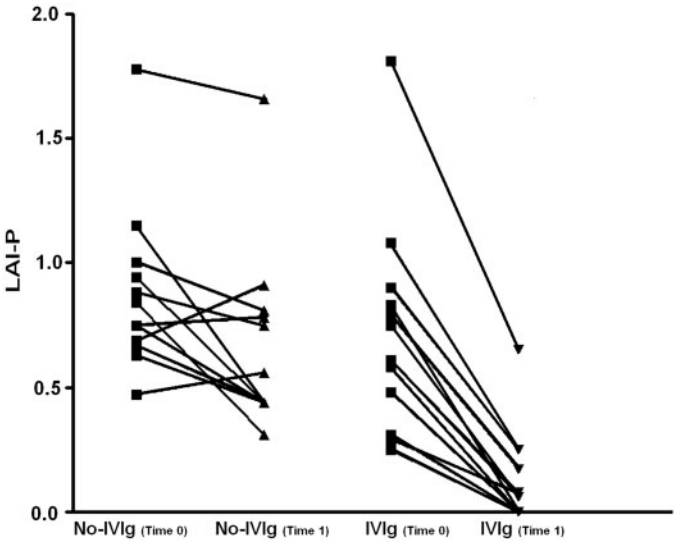

FIG. 1. LAI-P scale of the 12 SLE-RSA pregnant patients performed before IVIg therapy, at the beginning of pregnancy and after IVIg therapy, at the end of pregnancy in comparison with the LAI-P of the control group.

TABLE 6. Student's *t*-test (*P*-value) and Bonferroni's multiple comparison test (P_c-value) between the LAI-P values comparing the two groups

	Mean diff.	*t*	*P*-value	P_c-value	95% CI of diff.
IVIg at time 0 *vs* IVIg at time 1	0.595	4.258	<0.0001	<0.001	0.2089, 0.9811
IVIg at time 0 *vs* No-IVIg at time 0	0.1558	1.115	>0.05	>0.05	−0.2302, 0.5419
No-IVIg at time 0 *vs* No-IVIg at time 1	0.2142	1.533	>0.05	>0.05	−0.1719, 0.6002

Time 0: beginning of pregnancy; Time 1: end of pregnancy.

same figure LAI-P curves for each patient of the control group are represented. Mean LAI-P score at the beginning of pregnancy was 0.72 ± 0.43 (range 0.25–1.81) in IVIg group *vs* 0.88 ± 0.34 (range 0.47–1.78) in the controls. There was no statistically significant difference between LAI-P of the two groups at the beginning of pregnancy (Table 6).

Mean LAI-P during gestational period clearly diminished in patients treated by means of IVIg and, at the end of pregnancy, scored 0.13 ± 0.19 (range 0.00–0.65; $P < 0.0001$, $P_c < 0.001$, Table 6). In the control group, no significant variation in LAI-P score was observed and three patients worsened (Table 6). Mean LAI-P in the control group scored at the end of pregnancy 0.66 ± 0.37 (range 0.31–1.66).

TABLE 7. Two-way ANOVA test between the LAI-P values comparing IVIg and control groups at the beginning and at the end of pregnancy

Source of variation	df	Sum-of-squares	Mean square	*F*	Percentage of total variation	*P*-value
Interaction	11	0.6347	0.0577	1.15	7.06	0.4048
Patient response	11	1.522	0.1383	0.3887	16.92	0.9358
IVIg	1	1.964	1.964	39.16	21.84	<0.0001
Subjects (matching)	12	4.271	0.3559	7.095	47.487	0.0009
Residual	12	0.6019	0.05016			

Effect of IVIg therapy on LAI-P total variation (in percentage).

Two-way ANOVA analysis indicated that IVIg is the most important source of variation of LAI-P values (Table 7).

A narrative description of results obtained in Table 7 is as follows. Interaction between patient response and IVIg accounted for 7.06% of the total variance ($P = 0.4048$), thus there was a 40% chance of randomly observing so much interaction in an experiment of this size and the interaction was considered not significant. IVIg accounted for 21.84% of the total variance (after adjusting for matching), the *P*-value was <0.0001 and there was a <0.01% chance of randomly observing an effect this big (or bigger) in an experiment of this size. The effect of IVIg is considered extremely significant (Table 7).

No adverse reactions to IVIg, neither complications, were observed.

Discussion

Our study demonstrates that IVIg is an effective and safe treatment for pregnant patients affected with SLE even when affected with recurrent spontaneous abortion. In view of the aforementioned aspects, IVIg can be considered effective both on pregnancy outcome and on maternal clinical and laboratory features, which strongly ameliorated after IVIg therapy. IVIg can be also considered safe as no adverse reactions were observed, pregnancy was led without fetal complications, and newborns presented a satisfactory Apgar score. In all cases, IVIg was well-tolerated and pregnancies were extended until delivery was felt to be safe. In most patients, clinical manifestations and laboratory parameters promptly responded to IVIg therapy, and effects on overall disease activity were confirmed by the reduction in LAI-P score.

LAI-P was demonstrated to be a satisfactory activity index for SLE pregnancy. Statistical analysis was consistent and it is very interesting to observe the weight of IVIg effect on total variance of LAI-P within the two groups of patients.

Indeed, IVIg effects on SLE pregnancy were significant when compared with results from the control group (Fig. 1). These patients, treated by means of prednisolone and aspirin, did not achieve the same results of the IVIg group. Despite a similar condition at the beginning of pregnancy, these patients did not have any important clinical or laboratory improvement, as demonstrated by an overall LAI-P score substantially unmodified. Nonetheless, clinical picture (and consequently LAI-P score) worsened in three patients, and one required the usage of AZA.

IVIg not only modified the clinical picture of the patients but also the laboratory findings, anti-dsDNA antibodies included. These data are very important as anti-dsDNA is a very sensitive disease activity marker [23]. Very important was also the reduction of the anti Ro/SS-A and anti La/SS-B [6]. The transplacental passage of these antibodies from the mother has been linked to neonatal lupus erythematosus and to the severe condition of congenital heart block, that represents a serious and often fatal complication. Thus, reduction of anti Ro/SS-A and anti La/SS-B may signify an overall reduced risk of neonatal lupus erythematosus and congenital heart block [23]. LAC was the only parameter that appeared to remain unchanged. This could be ascribed to the low sensitivity of this functional assay and/or to

the low number of patients positive, apart from the possibility that IVIg themselves may be ineffective on LAC.

Considering the overall pregnancy outcome, 100% of successful deliveries were carried out in the IVIg group (75% in the control group). The only maternal complication in the IVIg group was mild pregnancy induced hypertension, a condition that did not interfere with pregnancy outcome and that was probably to ascribe to the obesity of the patient. These findings stress the importance of IVIg not only in SLE and RSA pregnant patients, but in the whole SLE pregnancy.

Different immunomodulatory effects have been reported for IVIg. These effects may be of potential benefit in patients with SLE, RSA and in SLE pregnancy. Among others, Fc-receptor blockade, regulation of complement, antigen neutralization, immunomodulation by reduction of autoantibody production [24, 25], anti-idiotypic interactions, effects on cell-mediated responses and changes in distribution and function of T-cell subsets [26], as it has been demonstrated that free GM-CSF blood concentration significantly increases after IVIg infusion [27], may act specifically in pregnant SLE patients.

Furthermore, IVIg may play its role, besides commonly recognized effects exerted in pregnant patients as blockage of transplacental transfer of IgG [28], by reducing overall disease activity in pregnant SLE patients, immunomodulating specific cells as dentritic cells and reducing NK cell levels, which are frequently associated with RSA [29–32].

The fact that SLE can worsen during pregnancy is not a surprise if we think of pregnancy as a Th1/Th2 cooperation phenomenon, with a shift towards a Th2 profile, and we consider the pathophysiology of SLE, where Th2 exert a fundamental role together with the involvement of Th2 cytokines as IL-4 and IL-10. IVIg affect cytokine production in T lymphocytes and monocyte/macrophages, suppressing pathogenic cytokines, reducing synthesis of IL-2, TNF-β, IL-3, IL-4, IL-10 and IL-5 [33, 34]. Currently, it is well established that commercial IVIg preparations contain anti-idiotypic antibodies against a variety of idiotypes [35]. It is of interest that previous studies on fractionated IVIg specific for, respectively, anti-DNA and anti- β_2GP-I anti-idiotypic antibodies showed specific activity for SLE and reproductive failure in APS patients when compared with the whole IVIg compound. This underscores the possibility to fractionate many specific anti-idiotypic Igs from the same batch of IVIg that may then be utilized in various autoimmune conditions, such as SLE, APS and RSA [36, 37].

In conclusion, we suggest that high-dose IVIg may be a safe and effective therapy for pregnant patients suffering from SLE, even in those who suffer from RSA. Although there have not been significant medical problems associated with the use of IVIg in SLE, one of the main limiting factors on its use has been its considerable cost. However, IVIg demonstrated to have mild adverse effects and usage of IVIg reduces or substitutes other treatments, such as prednisolone or immunosuppressive agents, which do not achieve the same results and may have severe adverse effects especially when in high doses both on mother and fetus, thus not always being biologically and economically convenient. It may be of interest to consider the potential role of IVIg as a short-term adjunctive treatment and a useful steroid-sparing agent in SLE patients during pregnancy. Further studies are warranted to clarify this issue.

Rheumatology key messages

- High-dose IVIg may be a safe and effective therapy for pregnant patients suffering from SLE and recurrent spontaneous abortion with or without APS.
- IVIg might be considered a useful drug-sparing agent in SLE pregnant patients.

Acknowledgements

We are grateful to Ann C. Fallon for the revision of the manuscript.

Disclosure statement: The authors have declared no conflicts of interest.

References

1 Petri M. Systemic lupus erythematosus and pregnancy. Rheum Dis Clin North Am 1994;20:87–118.
2 Cervera R, Font J, Carmona F, Balasch J. Pregnancy outcome in systemic lupus erythematosus: good news for the new millennium. Autoimmun Rev 2002;1:354–9.
3 Ioannou Y, Isenberg DA. Current concepts for the management of systemic lupus erythematosus in adults: a therapeutic challenge. Postgrad Med J 2002;78:599–606.
4 Mok CC, Wong RW. Pregnancy in systemic lupus erythematosus. Postgrad Med J 2001;77:157–65.
5 Tincani A, Rebaioli CB, Frassi M *et al.* Pregnancy Study Group of Italian Society of Rheumatology. Pregnancy and autoimmunity: maternal treatment and maternal disease influence on pregnancy outcome. Autoimmun Rev 2005;4:423–8.
6 Gayed M, Gordon C. Pregnancy and rheumatic diseases. Rheumatology 2007;46:1634–40.
7 Zandman-Goddard G, Levy Y, Shoenfeld Y. Intravenous immunoglobulin therapy and systemic lupus erythematosus. Clin Rev Allergy Immunol 2005;29:219–28.
8 Sherer Y, Shoenfeld Y. Intravenous immunoglobulin for immunomodulation of systemic lupus erythematosus. Autoimmun Rev 2006;5:153–5.
9 Shoenfeld Y, Katz U. IVIg therapy in autoimmunity and related disorders: our experience with a large cohort of patients. Autoimmunity 2005;38:123–37.
10 Sany J. Intravenous immunoglobulin therapy for rheumatic diseases. Curr Opin Rheumatol 1994;6:305–10.
11 Triolo G, Ferrante A, Accardo-Palumbo A *et al.* IVIG in APS pregnancy. Lupus 2004;13:731–5.
12 Clark AL, Gall SA. Clinical uses of intravenous immunoglobulin in pregnancy. Am J Obstet Gynecol 1997;176:241–53.
13 De Carolis C, Greco E, Guarino MD *et al.* Anti-thyroid antibodies and antiphospholipid syndrome: evidence of reduced fecundity and poor pregnancy outcome in recurrent spontaneous aborters. Am J Reprod Immunol 2004;52:263–6.
14 Levy Y, Sherer Y, Ahmed A *et al.* A study of 20 SLE patients with intravenous immunoglobulin, clinical and serologic response. Lupus 1999;8:705–12.
15 Wilson WA, Gharavi AE, Koike T *et al.* International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome: report of an international workshop. Arthritis Rheum 1999;42:1309–11.
16 Miyakis S, Lockshin MD, Atsumi T *et al.* International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost 2006;4:295–306.
17 Tan EM, Cohen AS, Fries JF *et al.* The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982;25:1271–7.
18 Petri M, Genovese M, Engle E, Hochberg M. Definition, incidence, and clinical description of flare in systemic lupus erythematosus a prospective cohort study. Arthritis Rheum 1991;34:937–44.
19 Ruiz-Irastorza G, Khamashta MA, Gordon C *et al.* Measuring systemic lupus erythematosus activity during pregnancy: validation of the lupus activity index in pregnancy scale. Arthritis Rheum 2004;51:78–82.
20 Reber G, Tincani A, Sanmarco M, de Moerloose P, Boffa MC. Standardization group of the European Forum on Antiphospholipid Antibodies. Proposals for the measurement of anti-beta2-glycoprotein I antibodies. Standardization group of the European Forum on Antiphospholipid Antibodies. J Thromb Haemost 2004;2:1860–2.
21 Brandt JT, Triplett DA, Alving B, Scharrer I. Criteria for the diagnosis of lupus anticoagulants: an update. On behalf of the Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibody of the Scientific and Standardisation Committee of the ISTH. Thromb Haemost 1995;74:1185–90.
22 Agostoni A, Aygören-Pürsün E, Binkley KE *et al.* Hereditary and acquired angioedema: problems and progress: proceedings of the third C1 esterase inhibitor deficiency workshop and beyond. J Allergy Clin Immunol 2004;114(3 Suppl):S51–131.
23 Meng C, Lockshin M. Pregnancy in lupus. Curr Opin Rheumatol 1999;11:348–51.
24 Pyne D, Ehrenstein M, Morris V. The therapeutic uses of intravenous immunoglobulins in autoimmune rheumatic diseases. Rheumatology 2002;41:367–74.
25 Clark AL, Branch DW, Silver RM, Harris EN, Pierangeli S, Spinnato JA. Pregnancy complicated by the antiphospholipid syndrome: outcomes with intravenous immunoglobulin therapy. Obstet Gynecol 1999;93:437–41.
26 Kessel A, Ammuri H, Peri R *et al.* Intravenous immunoglobulin therapy affects T regulatory cells by increasing their suppressive function. J Immunol 2007;179:5571–5.
27 Perricone R, De Carolis C, Giacomelli R, Guarino MD, De Sanctis G, Fontana L. GM-CSF and pregnancy: evidence of significantly reduced blood concentrations in unexplained recurrent abortion efficiently reverted by intravenous immunoglobulin treatment. Am J Reprod Immunol 2003;50:232–7.

28 Sultan Y, Kazatchine MD, Maisonneuve P, Nydegger UE. Antiidiotypic suppression of autoantibodies to Factor VIII (antihemophilic factor) by high-dose intravenous gammaglobulin. Lancet 1984;2:765–8.
29 Ruiz JE, Kwak JY, Baum L *et al.* Intravenous immunoglobulin inhibits natural killer cell activity in vivo in women with recurrent spontaneous abortion. Am J Reprod Immunol 1996;35:370–5.
30 De Placido G, Zullo F, Mollo A *et al.* Intravenous immunoglobulin (IVIg) in the prevention of implantation failures. Ann N Y Acad Sci 1994;734:232–4.
31 Perricone C, De Carolis C, Giacomelli R *et al.* High levels of NK cells in the peripheral blood of patients affected with antiphospholipid syndrome and recurrent spontaneous abortion: a potential new hypothesis. Rheumatology 2007;46:1574–8.
32 Perricone R, Di Muzio G, Perricone C *et al.* High levels of peripheral blood NK cells in women suffering from recurrent spontaneous abortion are reverted from high-dose intravenous immunoglobulins. Am J Reprod Immunol 2006;55:232–9.
33 Ruiz JE. Effect of intravenous immunoglobulin on natural killer cell activity in women with recurrent spontaneous abortion. Master Degree Thesis, Finch University of Health Science/The Chicago Medical School USA, 1995.
34 Dietrich G, Kaveri SV, Kazatchine MD. Modulation of autoimmunity by intravenous immunoglobulins through interaction with the function of the immune/idiotypic network. Clin Immunol 1992;62:S73–81.
35 Toubi E, Kessel A, Shoenfeld Y. High-dose intravenous immunoglobulins: an option in the treatment of systemic lupus erythematosus. Hum Immunol 2005;66:395–402.
36 Blank M, Anafi L, Zandman-Goddard G *et al.* The efficacy of specific IVIG anti-idiotypic antibodies in antiphospholipid syndrome (APS): trophoblast invasiveness and APS animal model. Int Immunol 2007;19:857–65.
37 Shoenfeld Y, Rauova L, Gilburd B *et al.* Efficacy of IVIG affinity-purified anti-double-stranded DNA anti-idiotypic antibodies in the treatment of an experimental murine model of systemic lupus erythematosus. Int Immunol 2002;14:1303–11.