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Original Article

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Pregnancy in women with pre-existing lupus nephritis: predictors of fetal and maternal outcome

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Abstract

Background. Only few data are available on pregnancy in patients with lupus nephritis (LN) diagnosed before conception. The aim of this study was to identify the risk factors for complicated pregnancy in women with pre-existing LN.
Methods. In a multicentre study, we collected data on 113 pregnancies occurring in 81 women with pre-existing biopsy-proven LN. Primary outcomes were fetal loss including perinatal death and renal flares during and 12 months after pregnancy. Univariate and logistic regression analyses were used to identify predictors of outcomes.
Results. Renal biopsy performed 7.2 ± 4.9 years before pregnancy showed the following WHO classes: 6 patients in II, 8 in III, 48 in IV and 19 in V. At conception, most patients were in complete (49%) or partial (27%) remission. There were nine spontaneous abortions, one stillbirth and five neonatal deaths. Thirty-one deliveries were preterm. Birth weight was <2500 g in 34 newborns. During pregnancy or after delivery, there were 34 renal flares, most of which (20) were reversible. Three patients had a progressive decline of glomerular filtration rate (one on dialysis). At logistic regression analysis, the pregnancy outcome was predicted by hypocomplementaemia at conception (RR 19.02; 90% CI 4.58–78.96) and aspirin during pregnancy (RR 0.11; 90% CI 0.03–0.38). Renal flare was predicted by renal status (partial remission RR 3.0; 90% CI 1.23–7.34, nonremission RR 9.0; 90% CI 3.59–22.57).
Conclusions. Pregnancy can be successful in most women with pre-existing LN, even for those with a severe renal involvement at onset. Renal flares during and after pregnancy are not uncommon and can be predicted by renal status assessed before pregnancy. Normocomplementaemia and low-dose aspirin therapy during pregnancy are independent predictors of a favourable fetal outcome.

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Keywords: fetal outcome; lupus nephritis; pregnancy; systemic lupus erythematosus

Introduction

Pregnancy in women with systemic lupus erythematosus (SLE) and nephritis is at risk of fetal and maternal complications [1]. SLE flares can occur during pregnancy especially in women with active disease at conception [2–6]. Severe consequences of renal flare during pregnancy and postpartum, including acute renal failure and maternal death, have also been described [5–10]. The long-term prognosis of lupus nephritis (LN) has improved over recent decades due to more effective therapeutic strategies and better patient surveillance. A high rate of complete or partial remission can be obtained in most patients and a favourable long-term outcome has been reported also for patients with diffuse proliferative LN [11]. Whether this improved prognosis can result in a more favourable pregnancy outcome and in a reduced risk for the mother has not been established.

In this multicentre retrospective study, we describe a large cohort of pregnancies in women with LN diagnosed by renal biopsy and treated before pregnancy. The aim of the study was to identify, among the clinical and laboratory characteristics assessed at the beginning of pregnancy, risk factors predicting fetal and renal maternal outcome.

Patients and methods

Subjects

Patients were enrolled from 1985 to 2004 by centres participating in the 'Rene e Gravidanza' initiative of the Italian Society of Nephrology (http://www.sin-italy.org). Patients referred to rheumatology centres participating in the 'Pregnancy' Study Group of Italian Society of Rheumatology and

managed in a multidisciplinary team were also included. Inclusion criteria were (1) diagnosis of SLE based on the American College of Rheumatology criteria [12], (2) renal involvement assessed by a renal biopsy, (3) pregnancy recorded after the onset of renal disease and (4) follow-up with disease monitoring and renal function assessment up to 12 months after pregnancy. Women who had elective abortion only were excluded. Pregnancies occurring before the diagnosis of LN were recorded but not included in the study. Histological features of LN were classified according to the WHO classification [13]. At first prenatal visit, data on medical history were recorded, including renal and extrarenal symptoms of SLE, treatment at the onset of disease, maintenance therapy and therapy at conception. Clinical and laboratory assessment at conception included antinuclear antibodies, anti-double-stranded DNA antibodies, lupus anticoagulant, anti-cardiolipin antibodies, immunoreactive C3 and C4, serum creatinine, uric acid, 24-h proteinuria, urinary sediment microscopy. Anti-double-stranded DNA antibodies, C3 and C4, serum creatinine, uric acid, 24-h proteinuria and urinary microscopy were repeated every 10–12 weeks during pregnancy, 1, 3, 6 and 12 months after pregnancy or whenever a flare-up was suspected. Laboratory tests were performed according to standard methods used in different laboratories ensuring quality control. The glomerular filtration rate (GFR) was estimated using the Modification of Diet in Renal Disease (MDRD) four-variable equation (based on serum creatinine, age, gender and race) and expressed in ml/min/1.73 m^2 of body surface area [14]. The MDRD equation was not used to estimate GFR during pregnancy. In all cases, a strict cooperation between nephrologists, rheumatologists and obstetricians was pursued in order to share information and clinical decisions. Data on six pregnancies were included in part in a previous report [5].

Definitions

- Spontaneous abortion: fetal loss before 24 weeks of gestation.
- Elective abortion: voluntarily induced termination of pregnancy.
- Stillbirth: intrauterine fetal death after 24 weeks of gestation.
- Neonatal death: live infant dying within 28 days after delivery.
- Peri-natal death is obtained as the sum of stillbirths and neonatal deaths.
- Total fetal loss: the sum of spontaneous abortion and perinatal death.
- Preterm delivery: live birth before the 37th week.
- Small for gestational age (SGA) infants were identified when the birth weight was below the 10th percentile of the Italian population according to gestational week at delivery.
- Low birth weight was defined as a liveborn weighing <2500 g.
- Hypertension was considered present if systolic blood pressure was >140 mmHg and/or diastolic blood pressure >90 mmHg in sitting position in three consecutive measurements, or if anti-hypertensive drugs were used.
- Preeclampsia: in women without baseline hypertension and proteinuria <300 mg/day, preeclampsia is defined as new onset hypertension and proteinuria >300 mg/day after 20 weeks' gestation. In women without hypertension and proteinuria >300 mg/day at baseline, superimposed preeclampsia is defined as new onset hypertension and doubling 24-h urinary proteins or urine/creatinine ratio after 20 weeks' gestation. In women with hypertension and proteinuria >300 mg/day at baseline, diagnosis of superimposed preeclampsia requires both worsening hypertension (increase of systolic or diastolic blood pressure of 30 mmHg or greater and 15 mmHg or greater, respectively, above baseline values) and doubling proteinuria. Diagnosis of preeclampsia was taken into consideration only in the presence of inactive urinary sediment (<5 red blood cells/hpf).
- Complete renal remission: proteinuria <0.2 g/24 h, inactive urinary sediment (<5 red blood cells/hpf ≤ 5 white blood cells/hpf, no cellular casts), GFR >60 ml/min/1.73 m^2.
- Partial renal remission: proteinuria from 0.2 to 1 g/24 h, GFR >60 ml/min/1.73 m^2.
- Renal flare-up: increase in urinary protein excretion of at least 2 g/ day if basal proteinuria was <3.5 g/24 h, or doubled if proteinuria was >3.5 g/24 h associated with microscopic haematuria (>5 red blood cell per hpf).
- Renal disease status categories: for each pregnancy, the following exclusive categories were identified before conception on the basis of clinical and laboratory data: (1) complete remission as defined above, (2) partial remission as defined above, (3) proteinuria >1 g/24 h, or GFR between 30 and 60 ml/min/1.73 m^2.
- Immunosuppressive therapy categories: treatment of LN at onset or during relapses occurring before pregnancies was categorized as follows: (1) steroids only, oral or pulsed; (2) steroids and azathioprine or steroids and hydroxichlorochine and (3) steroids and cytotoxic agents oral or pulsed. All patients were advised to avoid pregnancy if they were taking cytotoxic agents. At conception and during pregnancy, the category of no therapy was also considered.

Outcomes

Primary outcomes were fetal loss including neonatal death and excluding elective abortions and the occurrence of a renal flare-up during pregnancy and during the 12 months of follow-up. Secondary outcomes were low birth weight, SGA, preterm deliveries and renal disease status assessed 12 months after pregnancy.

Statistical analysis

Quantitative variables were reported as mean and SD, or median and range, depending on the distribution. Absolute and relative frequencies were used for categorical variables. The impact of clinical and laboratory characteristics on the outcomes was tested by univariate analysis using χ^2 or ANOVA as appropriate. The following variables recorded at conception were taken into account: age, interval between onset of nephropathy and pregnancy, period of

Table 1. Characteristics of patients

No. of pregnancies/no. of patients	113/81
Age at SLE diagnosis (mean ± SD)	21.2 ± 5.3
Age at renal biopsy (mean ± SD)	23.0 ± 5.2
Age at pregnancy (mean ± SD)	30.4 ± 4.9
Interval between renal biopsy and pregnancy (years)	7.2 ± 4.9
Renal biopsy WHO classification (no. of patients)	
II	6 (7%)
III	8 (10%)
IV	48 (59%)
V	19 (24%)
Serum creatinine (mg/dl)	0.88 ± 0.24
GFR (ml/min/1.73 m^2)	86 ± 21.9
Urinary protein (g/24 h)	0.63 ± 0.84
Arterial hypertension (no. of pregnancies)	17 (15%)
Hypocomplementaemia (low C3 and/or C4 level)	45/111 (40%)
Positive LAC or anticariolipin Ab	27/74 (36%)
Status at conception (no. of pregnancies)[a]	
Complete remission	56 (49%)
Partial remission	30 (27%)
Non-nephrotic proteinuria	11 (10%)
Nephrotic syndrome	3 (3%)
GFR >30 < 60 (ml/min/1.73 m^2)	13 (11%)

SLE, systemic lupus erythematosus.
[a]Mutually exclusive categories (see the Definitions section).

Table 2. Treatment regimens before and during pregnancy

Therapy at onset or at relapses[a] occurred before pregnancy (no. of patients)	
Steroid (oral and/or pulsed)	22 (27%)
Steroid and azathioprine or hydroxichloroquine	12 (15%)
Steroid and cytotoxic (oral and/or pulsed)	47 (58%)
Therapy at conception (no. of pregnancies)	
No therapy	24 (21%)
Steroid (low doses)	55 (49%)
Steroid and azathioprine or hydroxichloroquine	27 (24%)
Steroid and cyclosporine	7 (6%)
Therapy during pregnancy (no. of pregnancies)	
No therapy	22 (19%)
Steroid (low doses)	65 (58%)
Steroid and azathioprine or hydroxichloroquine	20 (18%)
Steroid and cyclosporine	6 (5%)
Peripartum steroid pulses[b]	52 (46%)
Low-dose aspirin[c]	68 (60%)

[a]Twenty-nine patients were treated for one or more relapses occurred before pregnancy.
[b]Regimens of peripartum pulses varied from 40 mg/day methylprednisolone given i.v. for 4–6 days to 500 mg/day methylprednisolone and i.v. for 3 days followed by resumption of previous regimen.
[c]100 mg/day from 10th–15th week to few days before delivery.

observation, WHO class of renal biopsy, presence of arterial hypertension, GFR, proteinuria, renal disease status category, hypocomplementaemia, immunosuppressive therapy at onset and at conception (category). Low-dose aspirin administered during pregnancy, specific therapy for LN during pregnancy and steroid pulses peripartum were also included in the analysis. Logistic regression was used to assess the predictive value of each variable on binary outcomes taking into account the interaction or confounding effect of the other covariates. Relative risk and 90% confidence intervals are reported.

Each pregnancy was considered as a separate observation since we considered the clinical status and therapy at conception or during the individual pregnancy as predictors of outcome. Analyses were performed using the SPSS version 13.0 (SPSS Inc. Chicago IL, USA) package.

Results

Characteristics of patients

One hundred thirteen pregnancies satisfying selection criteria were recorded in 81 Caucasian women with LN (Table 1). In all patients, renal involvement was confirmed by renal biopsy. Twenty-eight pregnancies were recorded in 19 of these women as occurring prior to the renal biopsy (3 elective and 7 spontaneous abortions, 2 stillbirths and 16 live births) but were not included in the study. The renal biopsy antedated pregnancy 7.2 ± 4.9 years. More than half of the patients had a diffuse proliferative pattern of glomerular lesions. Arterial hypertension and renal function impairment (GFR between 30 and 60 ml/min/1.73 m^2) were recorded at conception in 15% and 11% of pregnancies, respectively. Hypocomplementaemia was present in 40% of pregnancies. Lupus anticoagulant and/or anticardiolipin antibodies were positive in 27 of 74 (36%) pregnancies. At conception, complete and partial renal remissions were present in 56 (49%) and 30 (27%) of pregnancies, respectively. Extrarenal manifestations of SLE consisting in cutaneous or joint symptoms were observed in 14 pregnancies. At the onset of LN or during the course of renal disease before pregnancy, all patients had at least one course of high-dose steroid (oral or pulsed) or steroid and immunosuppressive agents (Table 2). The majority were treated with cytotoxic agents (cyclophosphamide oral or pulsed or chlorambucil). A median cumulative dose of cyclophosphamide of 8.5 g (range 0.4–26 g) was administered in 63 patients with a median interval from drug withdrawal and pregnancy of 4 years (range, 1 month to 19 years). Only one patient was taking cyclophosphamide 50 mg/day at conception, but the drug was stopped when the patient realized that she was pregnant. Twenty-four pregnancies began in patients who were without any therapy specific for SLE. Cyclosporine and low-dose steroid were given to seven patients at the time of conception and six of them continued this treatment during pregnancy. Peripartum steroid pulses were given in 52 pregnancies, and low-dose aspirin was given during 68 pregnancies.

Fetal outcome and pregnancy complications

There were four twin pregnancies that gave birth to seven live newborns and one stillbirth (Table 3). Apart from three elective and nine spontaneous abortions, the remaining pregnancies resulted in live births, but five newborns died within 28 days. Total fetal loss including neonatal death and excluding therapeutic abortion was 13%. Of the five neonatal deaths, one was due to cardiac malformation, one due to respiratory distress syndrome in a 33-week newborn weighing 1765 g, and the other three

Table 3. Outcome of pregnancy

Live births	104/114 (91%)[a]
Spontaneous abortion	9 (8%)
Elective abortion	3 (2.6%)
Stillbirth	1 (in a twin pregnancy)
Neonatal death	5/104 (5%)[b]
Perinatal death	6/105 (6%)[c]
Preterm delivery	31/101 (31%)
SGA[d] (excluding twins)	23/97 (24%)
Birth weight (excluding twins)	27<2500 (27%), 7 <1500 (7%)
Fetal malformation	2 (2%)
Caesarean section	59 (58%)[e]

[a]Including four twins (seven live births and one stillbirth) and excluding elective abortions.
[b]Liveborn infants died before 28 days of age of total liveborn infants including twins.
[c]Neonatal deaths plus stillbirth of the foetuses surviving >20 weeks of gestation, including twins.
[d]SGA: small for gestational age (see the Definitions section).
[e]Forty-eight for maternal and 11 for fetal reasons.

Table 4. Renal flares according to renal disease status at conception

Baseline renal disease status	No. of flares (%)[a]	No. of responses
Complete remission	8/56 (14)	5
Partial remission	10/30 (33)	7
Non-nephrotic proteinuria	5/11 (45)	3
Nephrotic syndrome	2/3 (66)	1
GFR < 60 (ml/min)	9/13 (69)	4
Total	34/113 (30)	20

[a]No. of pregnancies.

were due to respiratory distress syndrome in very low birth weight (700, 700, 670 g) neonates born between 25 and 31 weeks of gestation. Preterm delivery in these four pregnancies was determined by fetal distress in one and by severe superimposed preeclampsia in the other three cases. A non-life-threatening cardiac malformation was recorded in a second newborn. Of the two fetal malformations, one was from a woman who was treated with cyclophosphamide 7 years before and the other was from a patient treated with azathioprine 1 year before pregnancy. Both received low doses of steroid during pregnancy. Altogether, preeclampsia was diagnosed in 11 cases. In two patients, preeclampsia was associated with placental abruption and in two other patients with eclamptic seizures. The rates of premature deliveries and SGA were 31% and 24%, respectively. Most of the deliveries were by caesarean section.

Maternal outcome

Thirty-four renal flares were diagnosed, 17 during pregnancy and 17 during the 12-month follow-up period. They were less frequent in patients in remission than in those with proteinuria exceeding 1 g/24 h or with GFR <60 ml/min/1.73 m^2 (Table 4). After a new course of immunosuppressive therapy or an increase in steroid dose, a complete or partial recovery of renal symptoms in terms of proteinuria or renal function was recorded in 20 cases. Three patients had a progressive worsening of GFR. One had a flare-up at 32 weeks of gestation that ended by caesarean section at 33 weeks; she was treated postpartum with prednisolone pulses associated with plasma exchange, but progressed to end-stage renal failure and 3 months after delivery had to be treated with haemodialysis. The other two patients had a flare-up after delivery and were treated with prednisolone pulses and cyclophosphamide, but they did not recover the level of renal function they had before pregnancy. Nine flares occurred during or after the 24 pregnancies in patients who had no specific therapy for LN at conception; one was observed among 12 patients in complete remission, five among 8 patients in partial remission and three among 4 patients with proteinuria >1 g/24 h. All but four of these nine flares were reverted by therapy. Twelve months after pregnancy, renal status categories included 57 complete remissions, 23 partial remissions, 19 with proteinuria >1 g/24 h with GFR >60 ml/min/1.73 m^2, 14 with GFR <60 ml/min/1.73 m^2 (one on renal replacement therapy).

Table 5. Predictors of adverse fetal and maternal outcomes

	Univariate analysis[a]	Logistic regression analysis	
Predictors	*P*	RR (90% CI)	*P*
Pregnancy loss[b]			
Low-dose aspirin during pregnancy	0.006	0.11 (0.03–0.38)	0.003
Hypocomplementaemia (C3/C4)	0.001	19.02 (4.58–78.96)	0.001
Proteinuria	0.035		n.s.
Renal flare during or after pregnancy			
Proteinuria	0.000		n.s.
Clinical status at conception	0.000		0.000
Partial remission (urinary protein <1 g/day)		3.00 (1.23–7.34)	0.043
Urinary protein >1 g/day and/or GFR <60		9.00 (3.59–22.57)	0.000

[a]Chi-square or ANOVA. RR = relative risk.
[b]Spontaneous abortions and perinatal deaths.

Predictors of adverse fetal and maternal outcome

Hypocomplementaemia and proteinuria were significantly associated with unsuccessful pregnancies (spontaneous abortion or perinatal death) at univariate analysis; however, at logistic regression analysis only hypocomplementaemia was significantly a predictor of the adverse outcome (Table 5). Low-dose aspirin given during pregnancy had a protective role both at univariate and logistic regression analyses.

Among the different variables considered as possible predictors of the adverse renal outcome, proteinuria as a continuous variable was a predictor of the renal flare-up at univariate analysis but not at logistic regression analysis, where proteinuria was tested simultaneously with the categorization of patients in three groups (complete remission, partial remission, protenuria >1 g/24 h or GFR <60 ml/min/1.73 m^2). At logistic regression analysis, the

risk of developing a flare-up was ninefold higher for patients with proteinuria >1 g or GFR <60 ml/min/1.73 m^2 and threefold higher for patients in partial remission as compared with those in complete remission.

Discussion

A high risk of fetal and maternal complications has been reported in women in whom LN first appears during pregnancy [3,5,7,10]. In developed countries, however, the most common context in which a nephrologist has to face the issue of pregnancy in SLE patients is a woman with an established diagnosis of renal disease. Variable results have been reported on fetal and maternal outcome in SLE women with pre-existing diagnosis of renal involvement [5,6,10,15–18]. The rate of successful pregnancies excluding elective abortions ranged from 65% to 92% being less favourable in women with an active disease in one report [6], but not in others [5]. The rate of flares also varied widely ranging from 8% to 27% with some severe cases rarely evolving to maternal death [5,6,10]. However, some series included only a limited number of patients or did not evaluate risk factors with an adequate statistical analysis.

In our multicentre study, we describe fetal and maternal outcome of a large cohort of pregnancies in patients with an established clinical and histological diagnosis of LN. In most cases, pregnancy occurred many years after the onset of renal disease. All patients were assessed by renal biopsy that showed a prevalence of diffuse proliferative LN. Most had been treated with steroid and cytotoxic agents and a large majority were in complete or partial remission at the onset of pregnancy. In order to identify significant predictors of fetal and maternal outcome, we considered a large number of clinical and laboratory parameters, including complex items such as categories of renal status or the regimens used to treat LN in different periods of the disease. We found that hypocomplementaemia was the strongest predictor of an adverse pregnancy outcome evaluated by the sum of spontaneous abortion and perinatal death, while low-dose aspirin therapy during pregnancy was significantly associated with fetal and neonatal survival. Proteinuria, which has been reported as a risk factor of a poor fetal outcome [10,19] in our study, was associated with the adverse pregnancy outcome at univariate analysis, but was not found to be an independent risk factor at logistic regression analysis. Other studies have shown a significant association between hypocomplementaemia and fetal loss [20,21] or intrauterine growth retardation in SLE patients [22]. It is likely that both proteinuria and hypocomplementaemia represent signs of an active LN. A significant association between fetal loss and SLE activity at pregnancy has been found in many [3,5,10,24,25] but not all studies [21,25–27]. Other factors such as hypertension and positive antiphospholipid antibodies were found to be independent predictors of fetal loss [5]. In our study, the pregnancy outcome was not related to these items; however, only few patients were hypertensive at the onset of pregnancy, and antiphospholipid antibodies were not available in all patients.

In spite of the high number of liveborns, we observed a worrying number of neonatal deaths. Out of the five newborns who died before 28 days of life, three were growth retarded and delivered before the 32nd week due to preeclampsia superimposed on LN. Preeclampsia is more common in SLE patients than in general population [1] even for women with renal disease [16,18], although diagnosis of preeclampsia in patients with renal disease can be difficult and can coexist with renal flare-up [23]. Whether preeclampsia could be prevented by low-dose aspirin is a matter of debate, but there is some evidence supporting their use in a high-risk population [28,29]. In our experience, aspirin was associated with a favourable pregnancy outcome although in our study its prescription was not randomized, and our data could not demonstrate an efficacy in preventing preeclampsia. We have to register, however, a diffuse attitude among the participating centres towards the use of aspirin in view of the practically absent side effects of its use during pregnancy in LN patients.

The majority of our patients did not show significant changes in proteinuria and renal function during pregnancy or after delivery, while renal flares during or after pregnancy were observed in about one-third of cases. However, at follow-up, only three patients had a progressive loss of renal function. Renal flares were more likely to occur in patients with urinary protein excretion >1 g/24 h or GFR <60 ml/min/1.73 m^2, but they were also more frequent in patients with partial remission as compared with those in complete remission. This finding suggests frequent assessments and clinical surveillance even for patients with proteinuria ranging from 0.2 to 1 g/24 h. WHO class at renal biopsy was not relevant as a predictor of a feto-maternal outcome. This means that the histological pattern obtained in most cases some years before pregnancy has no influence on the course of pregnancy and of nephropathy. On the other hand, the prognosis of patients with proliferative LN, which in the past was a forerunner of a poor long-term outcome, has greatly improved during these last decades thanks to more appropriate therapeutic strategies and more accurate surveillance of patients [11].

Whether the pregnancy is a risk factor of LN flare-up cannot be inferred by our data since we did not plan a case-control study. Tandon *et al*. [30] compared the changes in the renal disease activity patterns in 78 pregnancies occurring in 53 women selected for the presence of LN at conception with those observed in 78 non-pregnant LN patients matched by age and renal manifestations at the beginning of the study, and they did not find significant differences in the percentage of patients who became active, remained active or became inactive over the study period. In another study, Moroni *et al*. [5] reported data on renal activity in 51 pregnancies recorded in 38 patients known to have LN before pregnancy and showed that the incidence of renal flare during pregnancy and 6 months after delivery was similar to that observed before pregnancy.

Since the clinical activity is a risk factor for fetal and maternal outcome, an important issue is the best treatment option to control LN during pregnancy and postpartum. Most of our patients continued the drugs they were given before. Very few patients were given oral or pulsed cyclophosphamide, and this was promptly stopped. The two cases of fetal malformation were apparently not related to LN therapy. We explored whether LN flares could be

related to therapy schedules, but no significant correlation was found. However, patients who were without any specific therapy and were not in complete remission showed a high rate of flare during or after pregnancy. Therefore, women who have discontinued LN treatment and who become pregnant should receive a careful monitoring and, if they are not in complete remission, resumption of therapy should be considered. Peripartum steroid pulses were administered in 52 pregnancies following the attitudes of individual centres without a well-defined rationale, but no protective role on the postpartum flares was found.

There are some limitations in our study. Most of the pregnancies were in women with normal renal function; therefore, we could not evaluate the outcome of pregnancy in patients with reduced GFR that is a predictor of a poor fetal and renal outcome when combined with proteinuria >1 g/day in pregnancies occurring in non-systemic chronic renal disease [31]. In addition, all our patients were Caucasian; therefore, our conclusion could not be translated to LN women of other ethnicities such as Afro-American who are known to be characterized by a poorer prognosis [32].

In summary, our data suggest that pregnancy can be successful in most women with pre-existing LN even after a long-standing renal disease and even for those who had at onset a severe renal involvement. In view of the relatively high number of neonatal deaths, pregnancies should be followed by a multidisciplinary team including nephrologists, rheumathologists and obstetricians experienced in high-risk pregnancies and deliveries should be planned in tertiary-care settings provided with neonatology intensive care units. Complete remission at the beginning of pregnancy is associated with a lower risk of fetal and maternal complications. Therefore, when LN develops in a young woman, an aggressive therapy, including cytotoxic agents for the more severe histological classes of renal involvement, should be prospected to obtain the minimum level of proteinuria before planning pregnancy. Renal flares during pregnancy and postpartum are not uncommon and should be recognized and treated adequately. Proteinuria at the onset of pregnancy is a reliable predictor of flare and of an unfavourable renal outcome after pregnancy. Low-dose aspirin seems to be beneficial to reduce the risk of an adverse fetal outcome.

Conflict of interest statement. D.M. is an employee of Fresenius Medical Care. All other authors declare that they don't have any conflict of interest.

(See related article by C. J. Day *et al*. Lupus nephritis and pregnancy in the 21st century. *Nephrol Dial Transplant* 2009; 24: 344–347.)

Appendix. Participating centres and investigators

Brescia, Spedali Civili, Clinical Immunology (A.T., M. Nuzzo)
Brescia, Spedali Civili, Nephrology (G.G., F.V.)
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Catania, Osp Garibaldi, Nephrology (I. Palidda)
Lecco, Osp Manzoni, Nephrology (C. Pozzi)
Milano, Osp Niguarda, Nephrology (L. Radaelli, A. Antonacci)
Milano, IRCCS-Croff, Nephrology (G.M., B. Gallelli, S. Finazzi)
Modena, Nephrology (S. Cimino)
Padova, Rheumatology (A.D., M. Rampudda)
Putignano, Nephrology (M. Giannattasio)
Roma, Univ. La Sapienza, Nephrology (G. Pecci)
S. Giovanni Rotondo, Nephrology (A. Del Giudice)
Siracusa, Osp Umberto I (G. Daidone)
Sondrio, Nephrology. (V. De Cristofaro, B. Pagliari)
Torino, Osp S. Giovanni, Nephrology (P. Stratta, L. Colla)
Tradate, Nephrology (P. Scalia)
Verona, Nephrology (L. Gammaro)
Gruppo di Studio 'Rene e Gravidanza' past coordinators, Italian Society of Nephrology (D. Manfellotto, D. Montanaro, L. Gesualdo, G. Daidone).

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