Has pregnancy any impact on long term damage accrual and on the outcome of lupus nephritis?

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Abstract

No data are available about the impact of pregnancy on the long-term outcome of lupus nephritis.

Thirty-two women with lupus nephritis with a 10-years follow-up after their first pregnancy ("pregnant group") and 64 matched controls with the same follow-up and who never had pregnancies ("controls") were compared for the occurrence of SLE flares, chronic kidney disease (CKD), and SLICC/ACR Damage Index (SDI**).** The same evaluations were done before and after pregnancy in pregnant group. The predictors of CKD and damage accrual in the whole population were studied.

All patients were Caucasians. All classes of lupus nephritis were represented. At conception and after 10-years, in both groups, less than 10% of patients had active renal disease (p:ns). Controls had more frequent arterial hypertension (p:0.025). Between the two groups there was no difference in SLE flares and in CKD free survival curves (P:0.6 and P:0.37) during the 10-year follow-up. In both groups, the temporal trend, based on annual evaluation, of glomerular filtration rate and serum creatinine shows a significant decrease and increase respectively. However, the pregnant group maintained persistently better values of renal function than controls for the whole follow-up (P:0.00001). There was no difference in the Kaplan and Meier CKD free survival curves. SDI did not increase significantly in pregnant group in comparison to controls. In the pregnant group, all the above mentioned clinical parameters were comparable before and after pregnancy.

Among the clinical basal characteristics, high serum creatinine and occurrence of SLE flares predicted CKD, whereas low levels of C3, pre-existing damage score, and occurrence of SLE flares predicted SDI increase. Pregnancy was not a predictor of CKD or SDI increase.

Carrying a pregnancy during inactive lupus nephritis, does not seem to increase the rate of SLE flares, worsen renal prognosis or increase SDI significantly in the very long-term.

Keywords Lupus npehritis, pregnancy, renal and extrarenal SLE flares, SLICC/ACR Damage Index, chronic kidney disease.

INTRODUCTION

1.1 Systemic lupus erythematosus is a chronic autoimmune disease that affects female patients at reproductive age. For many years, pregnancy has been discouraged in women with lupus, particularly in the presence of renal disease, due to the high risk of maternal and fetal complications **[1, 2].** During the course of the last decades, maternal and fetal outcomes have improved dramatically. This improvement is the result of many factors including the administration of more effective therapeutic schedules which are able to induce SLE remission, the planning of pregnancies during inactive disease and the intensive surveillance during pregnancy. In a recent multicenter Italian prospective study that included 71 planned pregnancies in lupus nephritis (LN) patients, followed by a multidisciplinary team between 2006 and 2013, fetal loss accounted for only 8.4% of pregnancies, renal flares for 19.7% of mothers, and pre-eclampsia and HELLP for 11.2%. All flares were mild and responsive to therapy and the manifestations of pre-eclampsia HELLP were promptly reversible. Immunological activity, arterial hypertension and BMI were the triggers of maternal complications **[3, 4]**. Apart from the risk of preeclampsia, the presence or the development of hypertension during gestation may have long-term consequences, being a well known risk-factor for future cardiovascular disease **[5-7]**.

However, the effects of pregnancy on lupus do not end immediately after delivery: renal and extra renal SLE flares can occur during the post partum **[8-10]**. Unfortunately, only one study in Taiwan evaluated over the long term the risk of end stage renal disease (ESRD) and of death in SLE pregnant patients **[11].** To the best of our knowledge, no data about the long term outcome of LN after pregnancy are available.

To make up for this lack of information, 10 years after the first pregnancy, we evaluate: i) the rate of renal and extrarenal SLE flares; ii) the development of arterial hypertension; iii) and of chronic renal disease (CKD); iv) the increase of damage accrual, v) the predictors of CKD and damage accrual in the whole population being studied (pregnant group plus controls). To achieve this goal we have selected in our LN cohort, all the patients who had a first pregnancy at least 10 years before the beginning of this study (December 2016). We have compared their outcome 10 years post-partum with that before pregnancy and that of a well matched LN woman who did not have pregnancies (1 pregnant patient/2 controls).

1.2 Material and methods

Thirty-two women with a diagnosis of SLE according to ACR criteria **[12]** and with biopsy proven LN nephritis, who had a first pregnancy after the diagnosis of nephritis and a follow-up after pregnancy of at least 10 years, "pregnant group", entered this observational study. All pregnancies have been followed by a team of nephrologists and gynecologists and the follow-up post pregnancy was followed in our Nephrological Unit.

Among the other LN patients followed in our Unit we selected 64 controls, "controls", (1 case/2 controls) matched to pregnant patients based on the following criteria:

- same age at diagnosis of LN ($\pm$ 5 years);
- same year of diagnosis of LN ($\pm$ 5 years);
- same ISN/RPS (International Society of Nephrology and the Renal Pathology Society) histological classification **[13]**;
- same duration of the total follow-up of pregnant patients evaluated from the diagnosis of lupus nephritis to ten years after pregnancy ($\pm$ 2 years);
- no pregnancy

1.2.1Definitions

- Time 0 (t0): for pregnant patients it is the beginning of pregnancy; for controls it is the time after the diagnosis of lupus nephritis that corresponds to the beginning of pregnancy in pregnant group.
- Time 10 (t10): 10 years after t0.
- *eGFR:* glomerular filtration rate measured with MDRD formula
- *Complete renal remission*: serum creatinine <1.0 mg/dl and creatinine clearance $\geq$ 60 and proteinuria < 0.5 g/24h and <5 urinary erythrocytes (UE)/ high power field (HPF).
- *Partial renal remission*: serum creatinine<1.0 mg/dl and creatinine clearance $\geq$ 60 ml/min < 1.2 mg/dl and proteinuria between 0.5-2 mg/dl (or reduction of 50% of proteinuria if nephrotic values at baseline
- *Chronic Kidney disease* (CKD): eGFR persistently < 60 ml/min and/or serum creatinine > 1 mg/dl
- *Arterial hypertension*: systolic blood pressure > 140 mm/Hg and/ or diastolic blood pressure >90 mm/Hg in sitting position in three consecutive measurements.

- *Proteinuric flares* were defined by increase in proteinuria of at least 2 g/day if basal proteinuria ≤ 3.5 g/day or doubled values is basal proteinuria > 3.5 g/day with stable renal function.
- *Nephritic flares* were defined by an increase in serum creatinine of at least 30% and over the basal value associated with active urinary sediment (>5 urinary erythrocytes/ high power field (HPF) and /or cellular casts) with or without an increase in proteinuria **[14]**.
- *Pre-eclampsia* was defined by i) new onset hypertension and proteinuria >300 mg/day after 20 weeks of gestation in women without proteinuria and hypertension, ii) new onset of hypertension and doubling of proteinuria in those with proteinuria but no hypertension, iii) worsening of hypertension (increase of systolic or diastolic blood pressure of 15 mmHg or more) and doubling of proteinuria in women with both proteinuria and hypertension **[15 Brown].**
- *Pre-term birth:* delivery before 37 weeks gestation.
- *Small for gestational age*: <10 percentile according to customized charts.
- SLICC/ACR Damage Index (SDI): evaluated according to Gladman eta al. **[16, 17]**.

1.2.2 Statistical analysis

Median and interquantile (IQ) range (25–75th percentile) together with mean and standard deviation were used as descriptive statistics. For continuous variables, the non-parametric Student t-test was used for assessing any difference between the two groups of patients, while the χ^2 test was used for dichotomised variables. Survival curves were drawn using the Kaplan–Meier estimate and compared using the log-rank test. Linear regression models were used to check for a temporal trend in eGFR and serum creatinine in controls and pregnant patients.

1.3 RESULTS

All patients were Caucasians. The median age at diagnosis of LN was 23.8 (IQ 20.6-28.1) years for the pregnant group and 26.7 (IQ 20.2-31.2) years for controls (p:ns). All classes of LN were represented with a prevalence of class IV. The characteristics of the two groups of patients at diagnosis of lupus nephritis and their outcome after the induction of therapy is reported in **supplementary Table 1**. The median duration of follow-up from the diagnosis of LN to pregnancy was 7.8 years (IQ 4.3-9.6) for the pregnant group and 7.2 years (IQ 4.2-9.7) for controls.

1.3.1 Characteristics at time 0 (conception time) of pregnant group and of controls (Table 1)

At time 0**,** nine percent of the pregnant group and six percent of controls had active renal disease, the other patients have been in complete remission for a mean period of 3±2.9 and 1.8±2.1years respectively and the SLEDAI-2k and SDI scores were low in both groups (4 and 0.16 in the pregnant group and 4 and 0.41 in controls respectively; p:ns). In comparison to controls, pregnant patients had significantly lower serum creatinine (0.65 vs 0.8 mg/dl, p:0.01) and higher GFR (105.9 and 80.76 ml/min, p:0.01) although the median values of these tests were in normal range in both groups. Arterial hypertension was significantly more frequent in controls (40.6% vs 15.6%, p:0.025). As expected, pregnant patients were receiving a less aggressive treatment: 34% were not being treated with steroids and immunosuppressive drugs in comparison to 10.9% of controls (p:0.01) and the daily dosage of oral prednisone was lower (5 vs 10 mg/day, p:0.03).

1.3.2 Outcome of pregnancy.

Twenty-nine out of 32 pregnancies (90%) were planned during clinical inactive LN. The median duration of pregnancy was of 37 weeks (IQ 35.5-38). Twenty-two pregnancies (72%) ended at term, in the other 10 cases delivery occurred preterm. Delivery was with cesarian section in 11 cases. During gestation, three patients (9.4%) had a renal flare and 2 (6.25%) pre-eclampsia. All babies were born alive, healthy and with a median body weight of 2980 g (IQ 2600-3200). Two babies (8.0%) were small for gestational age.

1.3.3 Outcome of SLE and of LN from t0 to t10 and the clinical situation at last observation (t10) of the pregnant group and of controls (Table 1).

During the post-pregnancy follow-up (from t0 to t10), 10.5 (IQ 10.2 -10.7) years for the pregnant group and 10.3 (IQ 9.9 -10.7) for controls, complete renal remission was maintained for more than 60% of the whole observation in both groups. Renal, extra-renal and total SLE flares were similar in the two groups, when evaluated in terms of percentage of affected patients (46.9% vs 48.4%, 15.6% vs 26.6% and 50% vs 53.1% respectively in the pregnant group and in controls; p:ns) or in flares free survival curves **(figure 1 a, b, c).** The percentage of patients who developed CKD in the pregnant group (6.2%) was not significantly different from that of controls (15.6%; p:ns). We evaluated, with a linear regression model, the temporal trends of eGFR and serum creatinine based on annual evaluation. The temporal trend of eGFR shows a significant decrease in both groups. However, throughout the follow-up, pregnant patients show eGFR values better than controls (p:0.00001) **(figure 2 a)**. As expected, the trend for serum creatinine shows a significant increase and, in this case too, the pregnant group maintained better values (p:0.00001) than controls (**figure 2 b).** De novo arterial hypertension occurred in 2 pregnant patients (6.2%) and in five controls (7.8%, p:ns).

At last observation (t10) all patients were alive. Only a minority of patients in both groups had active renal disease (6.2% of the pregnant group vs 1.6% of controls p:ns) and the median SLEDAI-2k was 3 in both groups. Similarly to the clinical situation at t0, median serum creatinine and GFR were normal in both groups but significantly better in the pregnant group than in controls (0.70 vs 0.90 mg/dl, p:0.03; and 89.6 vs 69.23 ml/min, p:0.02 respectively) and arterial hypertension was less frequent (21.9% vs 48.4%, p:0.02) in the pregnant group. No patients entered ESRD. Furthermore, in the two groups, the Kaplan and Meier CKD free survival curves were not different **(Figure 3**).

1.3.4 SLICC/ACR Damage Index from t0 to t10 (Table 2)

There were no significant differences between the pregnant group and controls in the mean value of SDI at t0 (0.16±0.37 vs 0.41±0.67 p:ns) as well as at t10 (0.34±0.78 vs 0.83±1.25 p:ns). At t0, SDI was 0 in 84.4% of the pregnant group, in comparison to 78.1% of controls (p:ns) and the score increased in 18.5% and in 26% respectively during the follow-up. Altogether, considering all patients irrespective of the basal SDI (0 or >0), 21.9% of the pregnant group and 32.8% of controls had a score increase from t0 to t10 (p:ns).

1.3.5 Outcome of SLE before and after pregnancy in the pregnant group

In the pregnant group, the clinical, laboratory and therapeutical characteristics at conception (t0) were not significantly different from those at last observation (t10) **(Table 3).** Comparing the period from diagnosis of LN to pregnancy with 10 years after pregnancy, the renal and extra-renal flares free survival curves were not significantly different **(Figure 1 d, e, f**).

1.3.6 Predictors of CKD and of SLICC/ACR damage index increase (Table 4)

Among the clinical characteristics at t0 we looked for the predictors of CKD and of SDI increase at t10. Considering the whole population being sudied, the only predictors of CKD were, higher serum creatinine (p:0.01) and lower GFR (p:0.03), and the occurrence of renal (p:0.01) and total (p:0.03) SLE flares during follow-up. Low C3 levels (p:0.02), SDI higher than 0 (p:0.01), development of renal (p:0.006) and total (p:0.008) SLE flares during follow-up predicted an increase of SDI at t10. Pregnancy was not a predictor of CKD and of SDI increase.

1.4 DISCUSSION

This retrospective cohort study was aimed at establishing the long-term impact of pregnancy on renal and extra renal SLE activity, on development of CKD and on the increase of damage accrual in LN patients. A number of studies have demonstrated that maternal and fetal complications occur

during pregnancy even in women with complete clinical remission of SLE and of LN **[3,4,9,10]**, but no data are currently available about the possible long-term complications in these women. This is the first study that tries to improve our knowledge in this field.

It is well known that glomerular hypertension does not occur in normal pregnancy, in spite of the increase both in GFR and blood flow. Indeed, dilatation of the efferent and afferent arterioles and renal blood flow increase more than the increase in GFR which results in a decreased filtration fraction **[18]**. Whereas, in pregnancies of women with chronic renal insufficiency increased filtration per nephron occurs. This adaptive response to nephron loss leads to glomerular hypertension and subsequent glomerulosclerosis with progressive renal function decline **[12-23]**. Studies on repeated renal biopsies, performed in LN patients in complete renal remission as well, have shown invariably an increase in glomerular sclerosis **[24]**. These data, despite normal renal function at conception, suggest that glomerular hypertension can occur during pregnancy in some LN patients with possible deterioration of renal function and/or development of hypertension in the long term.

To test these hypotheses, we have compared the outcome of LN during 10 years after pregnancy of 32 LN pregnant women with that of 64 matched controls, who have never had pregnancies. In the great majority of the pregnant group (as well as in controls), LN has been in remission for some years at the time of conception, only one patient had eGFR<60 ml/min (53 ml/min) and arterial hypertension was significantly less frequent than in controls. The outcome of pregnancy was quite good, with no fetal losses, few renal flares and preeclampsia during pregnancy.

Considering that the development of renal flares during the course of LN is a well-known predictor of bad long term renal outcome, first, we have evaluated the occurrence of flares in the two groups **[25-27]**. The LN course within the pregnant group does not seem worse after pregnancy as demonstrated by the renal and extrarenal flares free survival curves evaluated before and after pregnancy. Similarly, no differences were demonstrated in flares free survival curves between pregnant group and controls in post pregnancy follow-up.

On the other hand, in both groups, the temporal trend based on annual evaluation of eGFR and serum creatinine shows a significant decrease and increase respectively. However, the pregnant group maintained persistently better values of renal function than controls for the whole follow-up, a difference already present at the time of conception between the two groups. At last observation, all patients were alive and none had ESRD. Six percent of the pregnant group have CKD, a lower but not significantly different percentage from controls (15.6%). The similarity between the two groups was confirmed by the Kaplan and Meier CKD free survival curves. Furthermore, to assess definitively the role of pregnancy in CKD development, we looked for the predictors of CKD in the

whole population in study. We found that pregnancy was not a predictor of CKD occurrence. In agreement with other studies in LN, renal function at t0 and the occurrence of renal flares were predictors of CKD. **[14, 25-30]**. All these results seem to exclude, in this cohort of Caucasian patients with stable LN, a negative impact of pregnancy on kidney function 10 years after delivery.
The retrospective Nationwide Population-Based Cohort Study of **Chiu TF** et al **[11]** confirmed that pregnancy was not a predictor of ESRD in SLE pregnant patients in comparison to non pregnant SLE patients and pregnant and non pregnant non SLE women population. Actually, no significant difference in ESRD incidence was observed between pregnant and non-pregnant SLE patients. Moreover, pregnant SLE patients had a lower risk of overall mortality than non-pregnant SLE patients. In the Chiu TF cohort **[11]** as in ours, pregnant SLE patients had a better clinical condition at the baseline than SLE controls. This is not surprising because the majority of the pregnancies in our group were planned.
Arterial hypertension is a well known predictive factor of bad renal outcome in patients with LN **[25,26]** and it is associated with damage accrual progression and implicated in the pathogenesis of premature atherosclerosis in SLE **[31, 35]**. Furthermore, hypertensive disorders during gestation have long-term consequences, being a well known risk-factor for future hypertension, cardiovascular and renal complications **[5,7]**. Arterial hypertension was associated with the risk of ESRD in the Taiwan study **[11].** In our study, arterial hypertension was significantly more frequent in controls than in pregnant group both at t0 and at t10, and an increasing number of patients in both groups developed arterial hypertension during follow-up. However, we did not observe any difference in new onset hypertension between the two groups and arterial hypertension was not predictive of CKD in our cohort.

Finally, we evaluated if pregnancy influences damage accrual in LN. To achieve this goal we used SDI, a validated tool, which has been demonstrated to predict future mortality in SLE patients **[16, 17, 36]**. The short-term impact of pregnancy on damage accrual was evaluated in a subgroup of patients of the LUMINA cohort. In this study, the change in damage accrual from before the pregnancy to the first post-partum visit (in mean 14.4 months after pregnancy) was evaluated in 67 SLE women belonging to three different ethnic groups. Despite SDI after pregnancy being significantly higher than before, pregnancy *per se* did not predict damage accrual but was strongly associated with pregnancy duration, disease activity, damage prior to pregnancy and total disease duration **[37]**.
In our study, both groups had low values of SDI at t0, which slightly increased, without any significant difference in both groups, during the follow-up. In the pregnant group, the observed

increase in damage accrual after pregnancy in comparison to the basal value was not significant. Moreover, we searched for the predictors of damage accrual in our whole cohort. Low C3 levels, pre-existing damage score at t0, occurrence of renal and of total SLE flares during follow-up, but not pregnancy predicted damage accrual. These data seem to suggest that pregnancy *per se* does not influence SDI progression in the long-term.

Some limitations of this study should be clarified. First, it is a retrospective study that includes a low number of patients, all of which were Caucasian, therefore these conclusions are applicable solely to this ethnic group. Although controls were matched to the pregnant group for many features, controls had worse renal disease and more frequent basal arterial hypertension. These factors hinder a precise estimate of the real impact of some risk factors (for example, impact of hypertension on renal function deterioration). Nevertheless, we think that our results provide a useful indication for patients and clinicians and could be a stimulus for further prospective studies including a larger number of patients.

1.5 CONCLUSION

In this retrospective cohort study of LN patients we compared long term renal and extra-renal activity of lupus and damage accrual before and after pregnancy in pregnant women, and between pregnant and non pregnant matched patients. It emerged that pregnancy in the long-term does not cause an increase in the rate of renal and extrarenal flares of CKD and of damage accrual. These positive results could be attributed to inactive SLE and LN at conception, along with careful pre-pregnancy counselling and pregnancy being strictly monitored by a multidisciplinary team.

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Table 1: Clinical characteristics of lupus nephritis patients who had a pregnancy (Pregnant group) and controls (Controls) at conception (T0) and at the last observation (T10) .

	Pregnant group (32 pts)	**Controls (64 pts)**	**P**
CLINICAL AND LABORATORY FEATURES AT T0			
Duration of SLE from diagnosis to t0, years	9 (6.4-11.7)	9.1 (6.4-12.2)	0.81
Duration of LN from diagnosis to t0, years	7.2 (4.2-9.7)	7.8 (4.3-9.6)	0.91
Complete renal remission/ Partial renal remission/No remission, n pts (%)	25 (78)/4 (12.5)/3 (9.4)	43 (67.2)/17 (26.6)/4 (6.3)	0.27
Cronic Kidney Disease, n pts (%)	1 (3.1)	0	0.11
Arterial hypertension, n pts (%)	**5 (15.6)**	**26 (40.6)**	**0.025**
SLEDAI-2K	4 (2 - 5.25)	4 (2 – 5.25)	0.31
SLICC/ACR damage index, mean ± st. dev.	0.16 (± 0.37)	0.41 (± 0.67)	0.2
Laboratory Values			
Serum creatinine, mg/dl	**0.65 (0.60 - 0.80)**	**0.80 (0.70 - 0.9)**	**0.01**
eGFR, ml/min	**105.90 (81.75 – 115.63)**	**80.76 (68.10 - 91.6)**	**0.01**
Proteinuria, g/day	0.19 (0.00 - 0.36)	0.33 (0.12 - 0.6)	0.94
Proteinuria > 3.5 d/day, n pts (%)	2 (6.3)	3 (4.7)	0.75
Erythrocytes at urine sediment, n/ HPF	4 (0 - 5.25)	1 (0 - 5)	0.60
C3 < 90 mg/dl, n pts (%)	22 (68.8)	39 (60.9)	0.45
C4 < 15 mg/dl, n pts (%)	14 (43.6)	25 (39.1)	0.66
antiDNA pos, n pts (%)	22 (75.9)	30 (63.8)	0.27
Treatment			
No prednisone and immunosuppressive therapy, n (%)	**11 (34.4)**	**7 (10.9)**	**0.01**
Daily dosage of prednisone, mg	**5 (0-10)**	**10 (5-15)**	**0.03**
Immunosuppressive therapy, n pts (%) CYC/ MMF/ CSA/ AZA. n (%)	6 (18.8) 0/ 0/ 3/ 3	26 (40.6) 2/ 5/ 4/ 15	0.056
Hydroxycloroquine, n pts (%)	4 (12.5)	12 (18.8)	0.5
FLARES AND OTHER COMPLICATIONS FROM T0 to T10			
Renal flares/extrarenal flares/total flares, n pts (%)	15(46.9)/5(15.6)/16(50)	31(48.4)/17(26.6)/34(53.1)	0.68
Duration of complete remission (%), years	7.1 (67.6)	6.3 (61.2)	0.76
New onset hypertension from t0 to t10, n pts (%)	2 (7.4)	5 (13.2)	0.46
New onset chronic Kidney Disease from t0 to t10, n pts (%)	2 (6.3)	10 (15.6)	0.28
CLINICAL AND LABORATORY FEATURES AT 10			
Duration follow-up from t0 to t10, years	10.5 (10.2-10.7)	10.3 (9.9-10.7)	0.48
Complete renal remission/ Partial renal remission/No remission , n pts (%)	23(71.9)/7 (21.9)/2(6.2)	46 (71.9)/ 17 (26.5)/1(1.6)	0.43
Chronic Kidney Disease, n pts (%)	3 (9.4)	10 (15.6)	0.40
Arterial hypertension, n pts (%)	**7 (21.9)**	**31 (48.4)**	**0.022**
SLEDAI-2K	3.0 (1.0 - 5.25)	3.0 (1.0 – 5.00)	0.75
SLICC/ACR damage index, mean ± st. dev.	0.34 (± 0.78)	0.83 (± 1.25)	0.1
Laboratory Values			
Serum creatinine, mg/dl	**0.70 (0.68 - 0.83)**	**0.90 (0.76 - 1.00)**	**0.03**
eGFR, ml/min	**89.60 (75.87 - 96.68)**	**69.23 (59.89 - 85.36)**	**0.002**
Proteinuria, g/day	0.23 (0.14 - 0.46)	0.25 (0.10 - 0.43)	0.080
Erythrocytes at urine sediment, n/HPF	0.0 (0.0 - 1.75)	0.0 (0.0 – 1.75)	1.0
C3 < 90 mg/dl, n pts (%)	15 (46.9)	36 (56.2)	0.40
C4 < 15 mg/dl, n pts (%)	10 (31.2)	24 (37.5)	0.55
antiDNA pos, n pts (%)	19 (59.4)	31 (57.4)	0.86
Treatment			
No prednisone and immunosuppressive therapy, n (%)	**14 (43.6)**	**20 (31.3)**	**0.33**
Daily dosage of prednisone, mg	1.25 (0 - 5.3)	3.13 (0 - 5.3)	1.00
Immunosuppressive therapy, n pts (%) CYC/ MMF/ CSA/ AZA. n (%)	10 (15.6) 0 / 4/ 3 / 3	28 (43.8) 0/ 1/ 9/ 7	0.24
Hydroxycloroquine, n pts (%)	11 (34.4)	30 (46.9)	0.24

Legend: SLE: Systemic Lupus Erythematosus. LN: Lupus Nephritis. n pts: number of patients. SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000. SLICC/ACR damage index: Systemic Lupus International Collaborating Clinics/ College of Rheumatology Damage Index. eGFR: glomerular filtration rate measured with MDRD formula. st. dev.: standard deviation. CKD: Chronic Kidney Disease. HPF: High Power Field. CYC: cyclophosphamide. MMF: mycophenolate mofetil. CSA: cyclosporine. AZA: Azathioprine. n pts: number of patients

If not otherwise specified data are presented as median and 25° and 75° percentiles (interquartile ranges [IQR])

Table 2: “SLICC/ACR-DSI” damage Index at T0 and at T10 in the pregnant group and in controls.

	SLICC/ACR-DSI = 0 at t0			SLICC/ACR-DSI ≥ 1 at t0			SLICC/ACR-DSI at t10	
	Total	**Unchanged at t10**	**Increased at t10**	**Total**	**Unchanged at t10**	**Increased at t10**	**Unchanged**	**Increased**
Pregnant group, n pts (%)	**27 (84.4)**	**22 (81.5)**	**5 (18.5)**	**5 (15.6)**	**3 (60.0)**	**2 (40%)**	**25 (78.1)**	**7 (21.9)**
means ± st. dev.			1.2±0.4	1±0		2±0	0.1±0.3	From 0.3±0.5 To 1.4±0.5
Controls, n pts (%) /	**50 (78.1)**	**37 (74%)**	**13 (26)**	**14 (21.9)**	**6 (42.9)**	**8 (57.1%)**	**43 (67.2%)**	**21 (32.8%)**
means ± dev. st.			1.7±1.0	2±1		3±1	0.1±0.4	From 0.8±1.2 To 2.2±1.3
P	0.76	0.64		0.76	0.89		0.38	0.38

Legend: SLICC/ACR damage index: Systemic Lupus International Collaborating Clinics/ College of Rheumatology Damage Index. DSI: Damage Score Index. st. dev.: standard deviation.

Table 3: Characteristics of the pregnant group before and after pregnancy

	Before pregnancy (32 pts)	After pregnancy (32 pts)	p
Clinical Characteristics			
Complete renal remission/ Partial renal remission/No remission, n pts (%)	25 (78) 4 (12.5) 3 (9.4)	23 (71.9) 7 (21.9) 2 (6.2)	0.7/0.5/1.0
Chronic Kidney Disease (CKD), n pts (%)	1 (3.1)	3 (9.4)	1.0
Arterial hypertension, n pts (%)	5 (15.6)	7 (21.9)	0.75
SLEDAI-2K	4 (2 - 5.25)	3.0 (1.0 - 5.25)	0.13
SLICC/ACR damage index, mean ± st. dev.	0.16 (± 0.37)	0.34 (± 0.78)	0.23
Laboratory Values			
Serum creatinine, mg/dl	0.65 (0.6 - 0.8)	0.70 (0.68 - 0.83)	0.28
eGFR, ml/min	105.90 (81.75 – 115.63)	89.60 (75.87 - 96.68)	0.08
Proteinuria, g/day	0.19 (0 - 0.36)	0.23 (0.14 - 0.46)	0.88
Proteinuria > 3.5 d/day, n pts (%)	5 (15.6)	8 (25)	0.53
Erythrocytes at urine sediment, n/ HPF	4 (0 - 5.25)	0.0 (0.0 - 1.75)	0.11
Hemoglobin < 12 g/dl, n pts (%)	12 (37.5)	7 (21.8)	0.27
White blood cells < 4000/uL, n pts (%)	2 (6.3)	1 (3.1)	1.00
Platelets < 150000/uL, n pts (%)	0	1 (3.1)	1.00
C3 < 90 mg/dl, n pts (%)	22 (68.8)	15 (46.9)	0.13
C4 < 15 mg/dl, n pts (%)	14 (43.6)	10 (31.2)	0.44
ANA pos (≥1/80), %	70.6	72	0.21
antiDNA pos, %	75.9	59.4	0.27
Treatment			
No prednisone and immunosuppressive therapy, n (%)	11 (34.4)	14 (43.6)	0.88
Prednisone ± immunosuppressive therapy, n pts (%)	21 (65.6)	17 (53.1)	0.45
Daily dosage of prednisone, mg	5 (0-10)	1.25 (0 - 5.3)	0.50
Immunosuppressive therapy, n pts (%) CYC/ MMF/ CSA/ AZA. n (%)	6 (18.8) 0/ 0/ 3/ 3	10 (15.6) 0 / 4/ 3 / 3	0.39
Hydroxycloroquine, n pts (%)	4 (12.5)	11 (34.4)	0.07

Legend: n pts: number of patients. SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000. SLICC/ACR damage index: Systemic Lupus International Collaborating Clinics/ College of Rheumatology Damage Index. eGFR: glomerular filtration rate measured with MDRD formula. st. dev.: standard deviation. HPF: High Power Field. CYC: cyclophosphamide. MMF: mycophenolate mofetil. CSA: cyclosporine. AZA: Azathioprine. n pts: number of patients

If not otherwise specified data are presented as median and 25° and 75° percentiles (interquartile ranges [IQR])

Table 4: Predictors of CKD and of SLICC/ACR-DSI increase, evaluated among the clinical characteristics at conception (T10)

	CKD (13 pts)	**No CKD (83 pz)**	**p**	**Increased SLICC/ACR-DSI (28 pts)**	**Unchanged SLICC/ACR-DSI (68 pts)**	**P**
Demographic Characteristics						
Duration of SLE from diagnosis to T0, years	8.9 (8.3 - 11.3)	9.0 (6.2 - 12.3)	0.60	8.2 (6.0 - 10.3)	13.4 (6.5 - 13.0)	0.36
Duration of LN from diagnosis to T0, years	8.6 (5.3 - 10.3)	7.3 (4.1 - 9.5)	0.31	7.3 (4.0 - 9.0)	11.7 (4.2 - 9.9)	0.81
Clinical Characteristics						
Complete renal remission, n pts (%)	7.0 (53.8)	61.0 (73.5)	0.15	18.0 (64.3)	50.0 (73.5)	0.37
Active renal disease, n pts (%)	0	7 (8.4)	0.61	0.0	7.0 (10.3)	0.18
Nephrotic syndrome, n pts (%)	0.0	5.0 (6.0)	0.80	0.0	5.0 (7.4)	0.06
SLEDAI 2K	4 (4 - 10)	4 (2 - 5)	0.10	4 (2 - 8.3)	5.5 (20 - 4)	0.22
SLICC t0 > 0. n pts (%)	2 (15.4)	17 (20.5)	0.67	10 (37.7)	9 (13.2)	**0.01**
Pregnancy, n pts (%)	3 (23.1)	29 (34.9)	0.40	7 (25.0)	25 (36.8)	0.27
Laboratory Values						
Proteinuria ≥ 0.5, n pts (%)	6 (46.2)	22 (26.5)	0.15	10 (64.3)	18 (26.5)	0.37
Proteinuria mg/die	0.56 (0.22 – 1.21)	0.27 (0.06 - 0.50)	0.99	0.5 (0.1 – 0.6)	0.4 (0.1 – 0.6)	0.39
Serum creatinine, mg/dl	0.9 (0.8 – 1.0)	0.8 (0.7 - 0.9)	**0.01**	0.8 (0.7 - 0.9)	0.8 (0.7 - 0.9)	0.06
eGFR, ml/min	75.3 (63.9 - 87.2)	83.5 (74.2 – 101)	**0.03**	79.7 (69.0 - 89.1)	89.4 (75.6 - 103.5)	0.06
Erythrocytes at urine sediment, n/ HPF	0 (0 - 10)	0 (0 - 4.5)	0.96	1.0 (0 - 9)	5 (0 - 3)	0.68
Arterial hypertension, n pts (%)	7.0 (53.8)	24.0 (28.9)	0.14	12.0 (42.9)	19.0 (27.9)	0.16
Hemoglobin < 12 g/dl, n pts (%)	4	31	0.65	9.0 (13.2)	26.0 (38.2)	0.57
White blood cells < 4000/uL, n pts (%)	0	9	0.09	1.0 (3.6)	7.0 (10.3)	0.28
Platelets < 150000/uL, n pts (%)	2	6	0.36	4.0 (14.3)	3.0 (4.4)	0.09
C3, mg/dl	76 (54- 90)	81.5 (66.5 - 94.5)	0.34	76 (53.5 - 88.5)	87 (69 - 99)	**0.02**
C4 mg/dl	14 (11.7 - 40	17 (11 - 24)	0.29	14.5 (11. - 24.8)	15 (12. - 24.5)	0.86
APL Ab positve, n pts (%)	3/11 (27.3%)	22/80 (27.5%)	0.74	8/26 (30.7%)	17/65 (26.2)	0.93
Treatment						
Daily dosage of prednisone, mg	10.0 (5.0 - 10.0)	7.50 (3.13 - 12.50)	0.84	10.0 (5.0 – 13.1)	6.3 (2.5 - 11.6)	0.64
Immunosuppressive therapy, n pts (%) CYC/ MMF/ CSA/ AZA. n (%)	3.0 (23.1) 0/ 1/ 1/ 1	29.0 (34.9) 2/ 4/ 6/ 17	0.40	9.0 (32.1) 0/ 1/ 3/ 5	23.0 (33.8) 2/ 4/ 4/ 13	0.87
Hydroxycloroquine, n pts (%)	0	16 (19.3)	0.18	6 (21.4)	10 (14.7)	0.42
SLE flares between T0 and T10						
Renal flares, n pts (%)	11 (84.6)	35 (42.2)	0.01	20 (71.4)	26 (38.2)	0.006
Extra-renal flares, n pts (%)	3 (23.1)	19 (22.9)	0.73	10 (35.7)	12 (17.6)	0.10
Total SLE flares, n pts (%)	11 (84.6)	39 (47.0)	0.03	21 (75.0)	29 (42.6)	0.008

Legend: CKD: chronic kidney disease, SLE: Systemic Lupus Erythematosus. LN: Lupus Nephritis. n pts: number of patients. SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000. SLICC/ACR damage index: Systemic Lupus International Collaborating Clinics/ College of Rheumatology Damage Index. eGFR: glomerular filtration rate measured with MDRD formula. st. dev.: standard deviation. HPF: High Power Field. APL Ab: Antiphospholipid antibodies. CYC: cyclophosphamide. MMF: mycophenolate mofetil. CSA: cyclosporine. AZA: Azathioprine. n pts: number of patients

If not otherwise specified data are presented as median and 25° and 75° percentiles (interquartile ranges [IQR])

Figure 1: Kaplan-Meier estimate of overall survival without renal (A), extrarenal (B), renal and extrarenal (C) flares in the pregnant group and in controls from t0 to t10 and without renal (D), extrarenal (E), renal and extrarenal flares in pregnant patients before and after pregnancy.

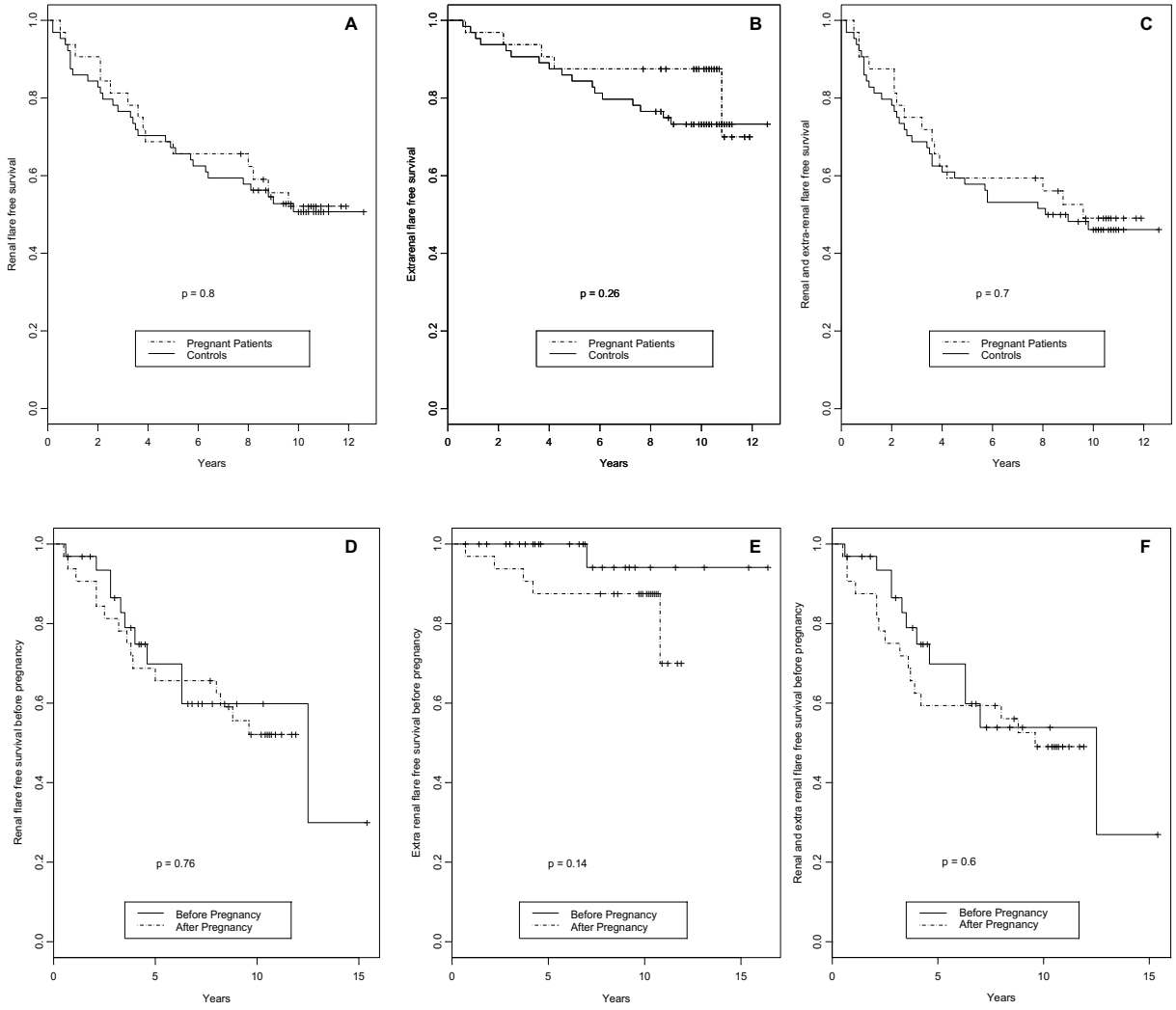


Figure 2: Temporal trend of eGFR (A) and serum creatinine (B) from T0 to T10 in the pregnant group and in controls

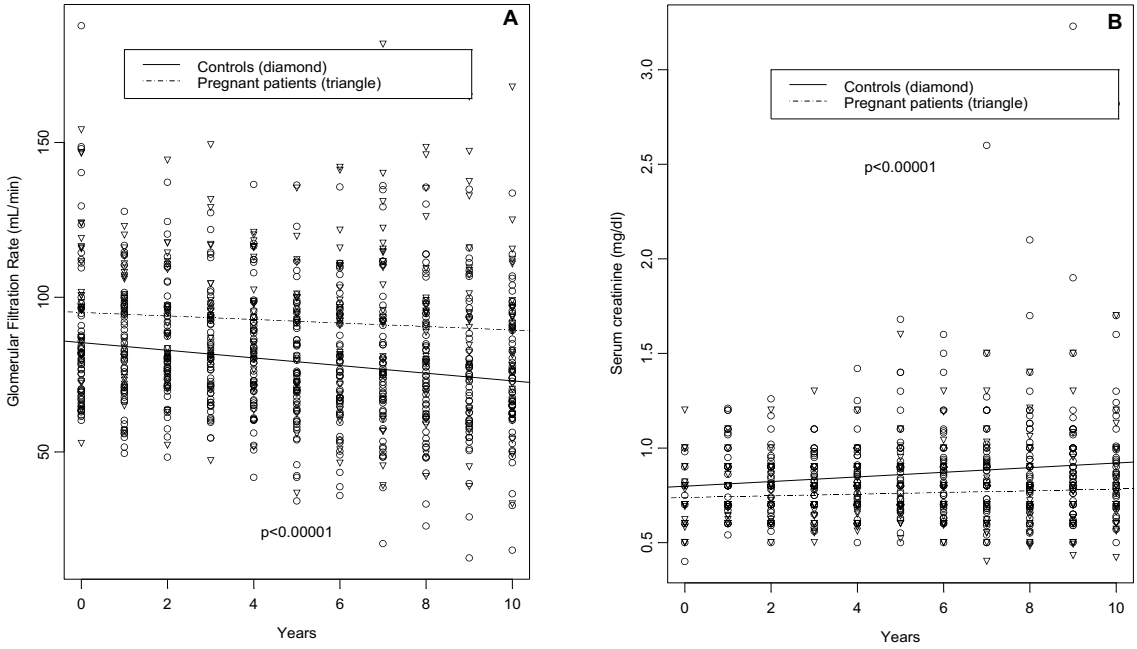
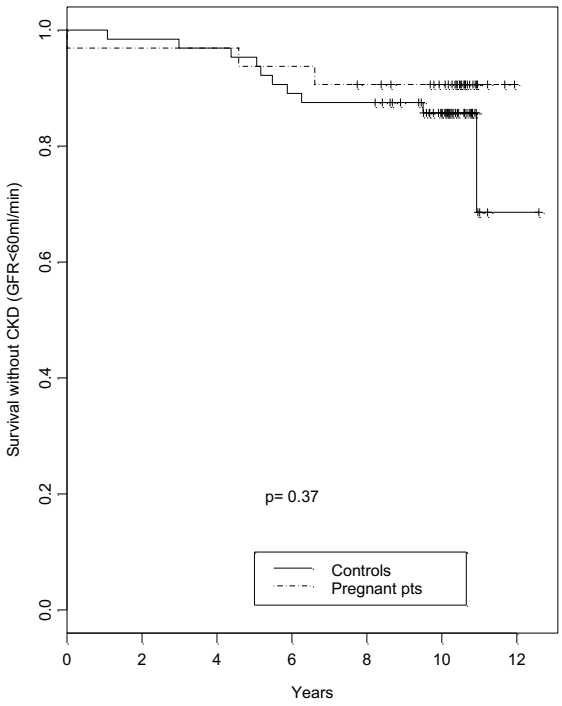


Figure 3: Kaplan-Meier estimate of overall survival without chronic kidney disease (CKD) in the pregnant group and in controls from T0 to T10.



Supplemental Table 1: Characteristics of Pregnant group and Controls at diagnosis of lupus nephritis and outcome after induction therapy.

	Pregnant group (32 pts)	**Controls (64 pts)**	**p**
Demographic Characteristics			
Age, years	23.8 (20.6-28.1)	26.7 (20.2-31.2)	0.20
Duration of SLE, years	0.1 (0.0 – 1.9)	0.2 (0.0 – 3.3)	0.60
Clinical Characteristics			
Histological class II/ III/ IV/ V / mixed, n pts	1 / 3 / 14 / 9 / 5	1 / 6 / 33 /18 / 6	
Activity index,	4 (0-8)	7 (2-9)	0.25
Chronicity index,	1 (0-2)	1 (1-3)	0.09
Arterial hypertension, n pts (%)	11 (34.3)	26 (40.6)	0.55
Articular involvement, n pts (%)	23 (71.9)	51 (79.7)	0.39
Constitutional symptoms , n pts (%)	19 (59.4)	39 (60.9)	0.88
Cutaneous involvement, n pts (%)	19 (59.4)	48 (75)	0.12
Serositis, n pts (%)	2 (6.2)	15 (23.4)	0.04
CNS involvement, n pts (%)	1 (3.1)	4 (6.2)	0.52
Laboratory Values			
Serum creatinine, mg/dl	0.8 (0.6-0.9)	0.9 (0.8-1.4)	0.048
eGFR, ml/min	91 (72.5-121)	72.6 (45.5-92.3)	0.018
Proteinuria, g/day	3.2 (2.15-4.9)	3.8 (1.9-5.5)	0.21
Erythrocytes at urine sediment, n/HPF	15 (5-32.5)	15 (5-40)	0.26
Anemia, n pts (%)	14 (44)	44 (69)	0.018
Leukopenia, n pts (%)	8 (25)	12 (18.7)	0.48
Thrombocytopenia, n pts (%)	1 (3.1)	12 (18.7)	0.03
APLs positvity, n pts (%)	8 (25.8%)	17 (28.3%)	0.16
C3 < 90 mg/dl, n pts (%)	24 (75)	52 (81.2)	0.48
C4 < 15 mg/dl, n pts (%)	21 (50)	44 (68.7)	0.76
Anti-DNA Ab posititivity, n pts (%)	26 (81.2)	50 (78.1)	0.72
Induction Therapy			
Steroids, n pts (%) MP pulses vs oral administration. n pts (%)	30(93.8) 27(84.4) vs 3(9.4)	62 (96.9) 41(64) vs 21 (32.9)	0.47 0.01
Immunosuppressive therapy, n pts (%) (CYC/ AZA/ MMF/ CSA/ RTX), n. pts	25 (78.1) 20 / 2/ 3/ 0 / 0	51 (79.7) 33 / 15/ 0 / 2/ 1	0.86
Hydroxycloroquine, n pts (%)	2 (6)	2 (3%)	0.47
Maintenance Therapy			
Prednisone alone, n pts (%)	18 (56)	37 (58)	0.88
Immunosuppressive therapy , n pts (%) AZA/ MMF/ CSA n	14 (43.7) 7 / 5 / 2	27 (42.2) 19 / 4/ 4	0.88
Hydroxycloroquine, n pts (%)	6 (18.7)	11 (17.2)	0.85
Renal Outcomes within two years			
Complete remission, n pts (%)	18 (56.3)	36 (56.3)	1.00
Partial renal remission: n pts (%)	13 (40.6)	24 (37.5)	0.77
No remission, n pts (%)	1 (3.1)	4 (6.2)	0.52

Legend: SLE: Systemic Lupus Erythematosus. n pts: number of patients. CNS: central nervous system. eGFR: glomerular filtration rate measured with MDRD formula. HPF: High Power Field. MP: methylprednisolone, CYC: cyclophosphamide. MMF: mycophenolate mofetil. CSA: cyclosporine. AZA: Azathioprine. n pts: number of patients

If not otherwised specified data are presented as median and 25° and 75° percentiles (interquartile ranges [IQR])