

LUPUS NEPHRITIS AND PREGNANCY. THE RHEUMATOLOGIST'S OPINION

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Abstract

In the presence of lupus nephritis, the pregnancy remains a challenging problem, requiring a multidisciplinary monitoring. Such pregnancies are considered as high risk similar to those with maternal and fetal potential complications. Thus, these pregnancies must be planned, after a multidisciplinary evaluation, performed by obstetrician, rheumatologist and nephrologist. Inactive disease for at least 6 months before conception, absence of hypertension, heavy proteinuria or important renal dysfunction are associated with good maternal-fetal outcomes. Lupus nephritis flare and preeclampsia may occur, associating a poor prognosis. Therapeutic regimens must be adapted, taking into account the teratogenic effects of the drugs.

Keywords: lupus nephritis, pregnancy, maternal-fetal outcome

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune inflammatory disease, which affects predominantly women of childbearing age (1).

Until the last two decades, the women diagnosed with SLE were advised to avoid pregnancy, because of high morbidity and mortality of mothers and adverse fetal outcomes (loss of the foetus in about 40% of cases). Nowadays, due to the novel therapies and a better management of this disease, the pregnancy is permitted, and the rate of pregnancy loss decreased to 17% (2,3).

One of the most important causes of morbidity in patients with SLE is renal involvement, known as lupus nephritis (LN). The prevalence of LN is about 29-82%, depending on the race/ethnicity (4). Pregnancy in women with LN remains a high risk one, with potentially maternal and fetal complications (5). Hypertension, the degree of proteinuria, and the value of glomerular filtration rate at the moment of conception, antiphospholipid syndrome represent

the risk factors associated with poor pregnancy outcomes in LN patients (6). Rahman et al. identified that LN, especially active form of the disease, represented the only significant factor associated with adverse pregnancy outcomes (7). Pregnancy-associated maternal-fetal risks increase along with the stage of chronic kidney disease (CKD) generated by the LN (8).

In order to avoid these maternal (preeclampsia/eclampsia, disease flares requiring teratogenic immunosuppressive therapy) and fetal complications (spontaneous abortions, fetal death, intrauterine growth restriction and preterm delivery), the pregnancy in LN patients must be planned, after a multidisciplinary consultation between rheumatologist, nephrologist, and obstetrician (9).

In clinical practice, two situations can be identified: the patients known to have SLE and LN before pregnancy, or, less commonly, diagnosed with SLE and LN during pregnancy (1,9). The definitions of the terms used in this paper are presented in Table 1 (6).

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TABLE 1. The definitions of the terms (5)

Term	Definition
Complete LN remission	proteinuria < 0.2 g/24 hours inactive urinary sediment GFR > 60 ml/min/1.73 m ²
Partial LN remission	proteinuria: 0.2-1 g/24 hours GFR > 60 ml/min/1.73 m ²
Active LN	active urinary sediment and/or proteinuria > 0.5 g/24 hours with/without elevation in serum creatinine (≥ 1.2 mg/dL) before 20 weeks gestation.
Active urinary sediment	≥ 5 red blood cells/high power field ≥ 5 white blood cells/high power field and/or ≥ 1 cellular cast
Inactive urinary sediment	< 5 red blood cells/high power field < 5 white blood cells/high power field no cellular casts

Renal function and pregnancy

During pregnancy, in healthy women appear structural (dilatation of the calices, renal pelvis, and ureters, especially on the left side) and hemodynamic changes (reduce in vascular resistance, increase in renal plasma flow and glomerular rate filtration), as early as 6 weeks after conception (10).

Increase of glomerular filtration rate by 50% is the most important change during normal pregnancy. Secondary to this increase, serum creatinine levels are reduced by the end of the pregnancy (the normal range of serum creatinine during pregnancy is between 0.4 and 0.6 mg/dl). A value of serum creatinine higher than 0,8 mg/dl has a significance of renal dysfunction. Another consequence of this glomerular hyperfiltration is increased proteinuria, significant proteinuria being defined as 300 mg or more/24 hour (11). Urinary excretion of albumin is normal in healthy pregnancy (12).

Increased glomerular filtration rate produces further kidney damage in patients with preexisting chronic kidney disease (CKD) (13).

During pregnancy, the severity of CKD is established based on serum creatinine or glomerular rate filtration. Early stage of CKD is defined by the serum creatinine level less than 1.4 mg/dL or creatinine clearance over 70 ml/min. Moderate CKD is characterized by the serum creatinine between 1.4 and 2.4 mg/dl (creatinine clearance 40 and 70 ml/min) and severe CKD is defined as serum creatinine over 2.4 mg/dl, or creatinine clearance less than 40 ml/min. The studies performed on CKD pregnancies suggested that the pregnancies in women with only

mild renal impairment, normal blood pressure, and no/minimal proteinuria, have much lower risks for accelerated progression during pregnancy and long term after delivery. Reduced renal function, hypertension, and important proteinuria before conception are associated with the risk of the further reduction of renal function after pregnancy (8,14).

Fertility and lupus nephritis

In women with SLE without prior Cyclophosphamide treatment, fertility is preserved. Cyclophosphamide therapy or severe CKD (baseline serum creatinine ≥ 3 mg/dl) contribute to impaired fertility (6,9). Mok et al. identified that the incidence of ovarian failure after Cyclophosphamide treatment was about 26%. By using multiple logistic regression, the authors demonstrated that the high cumulative dose of drug ($p = 0.02$) and increased age at the moment of treatment initiation ($p = 0.001$) represented the risk factors associated with the Cyclophosphamide-related infertility (15). In another study, Medeiros et al. found the incidence of ovarian failure after Cyclophosphamide exposure about 15.5%, the risk factors for this condition being represented by patients higher mean age ($p < 0.001$), longer duration of SLE ($p < 0.01$), and higher cumulative drug dose ($p < 0.05$). The authors reported that the relative risk for ovarian failure in SLE patients was 3.2, when the cumulative dose of Cyclophosphamide was higher than 10 g (16). The same results were reported by Appenzeller et al, too (17).

Timing and preconception period

Patients with LN need to plan their pregnancy, after a multidisciplinary evaluation (rheumatologist, nephrologists, obstetrician).

Pregnancy is permitted in patients with LN, if the following conditions are met: inactive SLE for 6 months before conception, inactive LN and renal function preserved (absence of hypertension, heavy proteinuria, or severe renal impairment). In the case of active NL, it is advisable to postpone the pregnancy for 12 months (the first 9 months representing the average time for achieving remission, and another 3 months for initiation maintaining therapy, in the context of a stable disease) (9,18). If the value of serum creatinine is over 2.8 mg/dl, the pregnancy will be contraindicated, because the chance of pregnancy success will be reduced to 20-30% and postpartum renal function decline will be a certainty (3).

However, pregnancy in LN patients remains a high risk one. It is estimated a high maternal risk (relative risk about 9 for NL flare during or after pregnancy), and high fetal risk (relative risk for fetal loss about 7.3, and for preterm delivery about 18.9) (19).

During pregnancy, therapeutic scheme may suffer some changes, because some drugs are allowed, while others do not. Cyclophosphamide, Mycophenolate mofetil and Methotrexate must be stopped at least 90 days pre-pregnancy. Corticosteroids (Prednisolone, in dose ≤ 10 mg/24 hours), Hydroxychloroquine, Azathioprine, Tacrolimus, and Cyclosporine A can be used in this period of SLE women life. If we refer to Hydroxychloroquine, this drug is not only allowed, but it is mandatory to be administered during pregnancy in SLE patients. Discontinuation of Hydroxychloroquine before conception was associated with the increased risk for SLE/LN flares during pregnancy (9,19).

Supplementation with folic acid is recommended during preconception period.

It is known the nephroprotective effects of renin-angiotensin blockers, and the favourable effects in LN, but these classes of drugs (angiotensin-converting-enzyme inhibitors and angiotensin II receptor blockers) are teratogenic and they must be stopped before pregnancy or soon after the pregnancy is confirmed. If the proteinuria rises over 1 g/24 hours without renin-angiotensin blockers, it will be reasonable to perform renal biopsy in order to confirm or to infirm the active LN. Renal biopsy requires rigorous control of blood pressure and normal coagulation parameters. This procedure is not advice

after 32 weeks of pregnancy. Side effects of this procedure (gross hematuria, perirenal hematoma) have the same incidence as in non-pregnant women (20). In the presence of histologically diagnosed active LN, the pregnancy will be postpone, after the complete remission will be achieved (9).

Some medical and immunological factors are associated with high maternal and fetal risks in LN pregnancies: active LN, arterial hypertension, important proteinuria (over 0.5-1 g/24 hours), reduced renal function (GRF < 40 ml/min), presence of lupus anticoagulant or anticardiolipin, anti $\beta 2$ glycoprotein I antibodies, platelet count less than 100,000/ μ l, hispanics or non-caucasians (21,22).

Pregnancy in patients with lupus nephritis

The pregnant female with LN must be rigorously monitorized during the entire pregnancy period and postpartum. The medical team will monitor the evolution of renal function (proteinuria, urinary sediment, serum creatinine, creatinine clearance), SLE activity and disease flares (levels of complement, antinuclear antibodies, anti dsDNA antibodies), evolution of blood pressure and early detection of preeclampsia signs (raise of blood pressure, proteinuria, and serum uric acid) (Table 2) (23).

The interrelation between pregnancy and NL refers to the following aspects: the impact of pregnancy on NL and the impact of NL/renal dysfunction generated by NL on maternal-fetal outcomes.

Germain and Nelson-Piercy showed in their study that pregnancy may accelerate decline in renal

TABLE 2. Maternal-fetal management in pregnant women with LN (23)

Obstetrician	First visit Monthly visits until 20 weeks Every 2 weeks visits until 24 weeks Every week visits until delivery	History taking Physical examination Ultrasonography in order to appreciate fetal development, and congenital heart block (in presence of anti-Ro52 antibodies)
Rheumatologist	First visit Monthly visits until delivery and postpartum	History taking Physical examination (signs of SLE flares) Antinuclear antibodies Anti-dsDNA, SSA/SSB, Sm, C1q (progressive rise) Complement C3, C4, CH50 (progressive decrease)
Nephrologist	First visit Monthly visits until delivery and postpartum	History taking Physical examination (signs of SLE flares) Urine exam Urinary protein/creatinin ratio Urinary albumin/creatinin ratio Urinary sediment Serum creatinine Glomerular filtration rate Serum uric acid
Neonatologist/ pediatric cardiologist	When signs of fetal distress or congenital heart block appear	In order to appreciate the appropriate therapeutic regimen

function and worsen hypertension and proteinuria, depending on the value of serum creatinine before conception. More severe renal dysfunction pre-pregnancy is associated with the further accelerated deterioration of renal function. If the pre-pregnancy value of serum creatinine was greater than 2.4 mg/dl, postpartum deterioration of renal function appeared in 60% of cases, reaching end-stage renal disease in 40% of cases (24). Imbasciati et al. reported that of 11% of NL patients in stage 3 of CKD, only 2% had evolved to a progressive deterioration in GFR and only 1% needed renal replacement therapy (18). Based on the study published by Bramham et al, the most important predictors of progression of renal dysfunction in pregnant NL patients were the pre-conception levels of GFR and proteinuria (GFR < 40 ml/min and proteinuria >1 g/24 hours were associated with permanent deterioration of renal function). The authors revealed that 10% of pregnant women with LN developed acute kidney injury, 3% of them presented a permanent decline in renal function without requiring dialysis, and 6% evolved to end-stage of chronic kidney disease or death (25). If the NL patients had multiple pregnancies before renal transplant, the risk of graft failure will be increased (26). The pregnancies of NL patients with renal transplant have the same evolution and the same risks as pregnancies in patients with renal transplant for other reasons (27).

The activity of LN and the severity of renal impairment determine the risks of maternal complications (flare of the SLE or/and LN, which can result in loss of renal function as well as an increase in both short- and long-term health risks associated with severe preeclampsia) and fetal ones (miscarriage, in presence of antiphospholipid syndrome, prematurity, intrauterine growth restriction, neonatal death) (6). Carmona et al. revealed that histological type of LN may influence the pregnancy outcomes. Type III and IV of LN are more frequently associated with hypertension and superimposed preeclampsia, having poor pregnancy outcomes than type II, or V. (27). Based on study of Germain and Nelson-Piercy, it was demonstrated that the reduced kidney function is associated with frequent maternal-fetal complications. If the serum creatinine before pregnancy is over 2.8 mg/dl, the rate of pregnancy success will be only 20-30%, maternal complication will appear in 85% of cases, 60% of babies will be growth restricted, and 70% of them will be preterm (24).

A study, performed by Imbasciati et al. on 113 pregnancies in 81 women with LN (49% in complete

remission and 27% in partial remission), described that the LN flares appeared in 34 cases and preeclampsia in 11 cases. These flares were associated with more severe renal disease and partial remission of LN, at the moment of conception. Pregnancy outcomes were represented by: 91% live births, 8% spontaneous abortions, 2.6% elective abortions, one stillbirth, 5% neonatal deaths, 6% perinatal deaths, and 31% preterm deliveries (due to preeclampsia, or worsening of renal function). Birth weight was < 2,500 g in 34 newborns (27 babies < 2,500 g, and 7 babies < 1,500 g). Fetal malformations were identified in 2% of cases. The pregnancy outcomes were predicted by hypocomplementaemia at conception (RR 19.02; 90% CI 4.58-78.96) and aspirin administration during pregnancy (RR 0.11; 90% CI 0.03-0.38) (18).

In their systematic review of 37 studies spanning a long period of time, between 1980-2009, Smyth et al. included 2751 pregnancies from 1842 SLE patients. The authors reported SLE flare in 25.6% of cases, hypertension in 16.3% of patients, LN in 16.1%, preeclampsia in 7.6% and eclampsia/stroke or death in approximately 1% of them. Active LN at the moment of conception, history of prior LN, and presence of antiphospholipid antibodies were associated with maternal hypertension ($p < 0.001$, respective $p < 0.029$), but only prior LN was associated with an increased risk for preeclampsia ($p < 0.017$). The poor pregnancy results were identified in 23.4% of women; among them the authors described: prematurity (34.9%), miscarriage (3.6%), neonatal deaths (2.5%), intrauterine growth restriction (12.7%) (28).

Based on Bramham et al. study, several factors contribute to pregnancy outcome in NL patients: SLE and NL activity, levels of renal function, presence of hypertension, proteinuria and antiphospholipid antibodies/antiphospholipid syndrome before conception. Quiescent SLE and LN, serum creatinine < 1.4 mg/dl, normal blood pressure and proteinuria < 0.5 g/24 hours are associated with favorable maternal-fetal outcome (25).

Predictors of Pregnancy Outcomes in Systemic Lupus Erythematosus and Antiphospholipid Syndrome (PROMISSE) study, including only patients with inactive LN at the moment of conception, revealed that the adverse pregnancy outcomes were represented by: miscarriage (4%), neonatal death (1%), preterm (9%), intrauterine growth restriction (10%). In patients stratified as low risk (caucasians,

TABLE 3. Differential diagnosis between LN flare and preeclampsia (2,9)

Clinical/biological feature	Preeclampsia	Lupus nephritis flare
Onset of hypertension	After 20 weeks of pregnancy	Any time during LN pregnancy
Proteinuria	Increased	Increased
Urinary sediment	Inactive	Active (dysmorphic erythrocytes, red cells casts)
Urinary calcium/24 hours	< 195 mg/dl	≥ 195 mg/dl
dsDNA levels	Normal	Increased (progressive rise)
Complement (C3, C4, CH50) levels	Normal	Decreased (progressive decrease)
Serum uric acid	Increased	Normal
Aminotransferase activity	Increased	Rarely increased
Extrarenal signs of SLE	Absent	Present

without arterial hypertension or antiphospholipid syndrome, platelet count of at least 100.000/mm³), adverse pregnancy outcomes appeared in 7.8% of them, compared with patients with high risk, where adverse pregnancy outcomes appeared in 58% cases. Flare of LN was reported in 2.3% of cases (22).

Moroni et al. showed that in 71 pregnancies of women with LN, maternal complications were represented by: preeclampsia (8.4%), and flare of LN (19.7%), whereas fetal complications were represented by: miscarriage (8.2%), preterm (30.1%), intrauterine growth restriction (16.4%). 79.8% of women were in complete remission and the remaining of 20.2% had a mild LN before conception. Renal flares were preceded by low levels of C3 and high levels of dsDNA. Preeclampsia was met in patients with prior LN with longer disease duration and hypertension. Adverse pregnancy outcomes were mentioned in patients with active LN at conception, arterial hypertension, antiphospholipid syndrome (especially in presence of lupus anticoagulant), high disease activity (measured by SLE-P-DAI score), LN with many flares before conception (29).

LN flare is defined by: active urinary sediment with increase of serum creatinine over 30%, or worsening proteinuria (increase by 2 g/24 hours, if baseline proteinuria was < 3.5 g/24 hours or doubling of proteinuria if baseline proteinuria was ≥ 3.5 g/24 hours) (6).

The incidence of LN flares during pregnancy or in postpartum period is between 1.5% and 83%. Renal flares occurs more frequently in women with active disease at conception (proteinuria ≥ 500 mg/24 hours, serum creatinine ≥ 1.2 mg/dl), the relative risk of flare in active LN is 9 (90% CI 3.59-22.57), and in partial remission is 3 (90% CI 1.23-7.34 (5,18). Severe flares are rarely met during pregnancy in women with SLE. LN flare can generate severe complications, including acute kidney injury, pro-

gressive loss of renal function to end-stage renal disease, preeclampsia, even maternal and fetal deaths (3,30).

During pregnancy, proteinuria may increase and hypertension may appear or aggravate. In this situation, it is very important to establish the etiology of these changes: LN flare or preeclampsia, because the treatment is totally different (9).

Preeclampsia appears in 13-35% of LN pregnancies, compared with 5-8% of pregnancies in the general US population. It is associated with active LN, hypertension and poor maternal-fetal prognosis (31). Distinctive features of LN flare and preeclampsia are presented in Table. 3. But the real challenge is represented by the association of these two conditions (superimposed preeclampsia on LN flare). In the first part of pregnancy, appearance or worsening of proteinuria and hypertension almost always means LN flare. In addition, signs of SLE activity (rising titer of dsDNA antibodies, reduced value of complement) and LN activity (haematuria with dysmorphic erythrocytes, especially acanthocytes and red cell casts) contribute to differentiate these two conditions. If the appearance/worsening of proteinuria, hypertension, and impaired renal function are found later in pregnancy (between the 26th and 40th weeks of gestation), differentiation between preeclampsia and LN flare will be difficult. But it is known that LN flare increases the risk of preeclampsia. If the LN patients present proteinuria and hypertension in early gestation, any sudden increase in proteinuria and/or hypertension, or the development of Hemolysis, Elevated Liver enzymes, Low Platelet count (HELLP) syndrome will establish the diagnosis of superimposed preeclampsia on LN. The cut-off value of serum uric acid of 5.5 mg/dl may differentiate preeclampsia (serum uric acid > 5.5 mg/dl), from isolated LN flare (serum uric acid ≤ 5.5 mg/dl) (5,31,32).

The novel biomarkers associated with preeclampsia (vascular endothelial growth factor receptor, placental growth factor) can differentiate preeclampsia from LN flare. Preeclampsia is associated with an altered maternal pattern of circulating placentally derived proteins which contributes to regulation of angiogenesis such as sFlt-1 (soluble fms-like tyrosine kinase 1) and PlGF (placental growth factor). It was demonstrated that in preeclampsia, the ratio between these two biomarkers has increased values. The sFlt-1:PlGF ratios > 85 (at 28 weeks of gestational age), and > 110 (at 36 weeks of gestational age) are associated with the development of preeclampsia (33).

Ultrasonographic fetal monitoring is recommended in all SLE pregnancies and includes: Doppler ultrasonography of the umbilical artery, uterine arteries, ductus venosus, middle cerebral artery. Using Doppler ultrasonography, the reduction of cerebro-placental ratio is associated with poor perinatal outcomes. In mothers who are positive for anti-Ro/SSA, anti-La/SSB antibodies, fetal cardiac ultrasonography is necessary to be performed at 16-18 weeks of gestation, in order to detect cardiac complications of neonatal lupus (19).

Treatment of lupus nephritis during pregnancy

The objectives of LN treatment during pregnancy are represented by: maintaining the remission of SLE/LN, preserving renal function and preventing the progression of renal dysfunction, recognition and prompt treatment of SLE/LN flares and preeclampsia (32).

Therapeutic regimens used in LN pregnant women are reduced, because of teratogenic effects of many immunosuppressive drugs.

The drugs used in therapy of LN which are considered to be safe in pregnancy are: glucocorticoids (Prednisone ≤ 10 mg/24 hours, during the first trimester), and Hydroxychloroquine.

Other class of drugs, compatible with pregnancy, are: Azathioprine (maximum 2 mg/kg/24 hours), Cyclosporine (risk of maternal nephrotoxicity), and Tacrolimus (risk of gestational diabetes) (34).

Glucocorticoids in low doses are used in LN pregnancies, in order to maintain the remission. Only 10% of Prednisolone dose crosses into fetal circulation, if the maternal dose of Prednisone is under 20 mg/24 hours, and the side effects on the foetus are negligible. High doses of corticoids used for a long period during pregnancy in LN women are

associated with an increased risk of maternal diabetes, hypertension, preeclampsia, premature rupture of membranes and infections (especially urinary tract infections). Previous results of oro-facial clefts induced by corticoids are not confirmed by the latest studies (3,20,35).

Given during pregnancy, Hydroxychloroquine diminished the risks of SLE/LN flares and thrombosis, being associated with better long-term kidney survival. The studies performed by Clowse et al. and Koh et al. confirmed that facts during the LN pregnancies (36,37). The data from PROMISSE study revealed that the risk of babies congenital heart block is reduced by 50% in LN mothers who have anti-Ro52 antibodies (38). The side effects of Hydroxychloroquine, including miscarriage, congenital defects, visual or hearing defects, intrauterine growth restriction or fetal death, are not increased. This drug will not be interrupted during pregnancy, and will be given to all LN women, who have not taken it before pregnancy (29,39).

By using Azathioprine in SLE/LN, favorable results were reported, such that this drug can be prescribed in this category of patients. This drug acts as a steroid-sparing agent. No adverse fetal effects were reported during many years of its use (9,19).

Calcineurin inhibitors are represented by Cyclosporin and Tacrolimus. Cyclosporin is safe in pregnancy, but can produce mother nephrotoxicity and preeclampsia; Tacrolimus is associated with gestational diabetes. Thus, using these drugs requires regular monitoring of mothers (20).

In order to reduce the risk of preeclampsia appearance, it is advised to add Aspirin in low dose by 12 weeks of pregnancy. In case of heavy proteinuria, or antiphospholipid syndrome with prior thrombosis, it is recommended to administrate low molecular weight heparin. Calcium and vitamin D supplementation is also indicated (9).

LN flares require different treatment, depending on the severity and the moment of occurrence during pregnancy. If the flare appears in the early pregnancy, termination of it will be an adequate option, in order to treat and to achieve complete remission. If the woman does not accept the termination of pregnancy, corticosteroids and immunosuppressive drugs will be the therapeutic solution.

Mild LN flares are treated by corticosteroids (Prednisolone 0,5 mg/kg/24 hours, with the aim to taper as rapidly as possible) associated with Hydroxychloroquine. In moderate/severe flares, high-dose

of corticosteroids, as pulse-therapy (for 3 days), will be given for a rapid effect, continued with Prednisolone orally (0,5 mg/kg/24 hours). Hydroxychloroquine is required in all SLE women. Azathioprine (up to 2 mg/kg/24 hours) is added to corticosteroids. Tacrolimus may be an alternative to Azathioprine in LN during pregnancy. This drug acts as steroid sparing, contributing to rapid reduction of proteinuria, due to its effects on podocyte stabilization. The study, performed by Webster et al. on 9 pregnant patients with LN flare, showed favorable results (achieving LN remission) by using this drug during pregnancy, at serum levels between 5-8 ng/ml (9, 40). Steroids and Tacrolimus are associated with an increased risk of maternal gestational diabetes, requiring continuous monitoring during pregnancy (9).

Cyclophosphamide and Mycophenolate mofetil are contraindicated in LN pregnancies. In the second and third trimester of pregnancy, if the LN is active, non-responsive to other therapeutic regimens (rapid progressive renal failure), Cyclophosphamide will be administered, with all its risks (19).

In the absence of high risk maternal situations (preeclampsia/eclampsia/HELLP syndrome) or signs of fetal distress, the birth will be scheduled after the 37th week of pregnancy. Cesarean section should be reserved for obstetrical indications (9,19).

Continuous rheumatological and nephrological monitoring is required during the postpartum period, for early detection of LN flare (9,19).

Contraception and lupus nephritis

Prescribing contraceptive measures in LN patients remains a challenging problem, because of the disease itself and the disease associated comorbidities. But, by using of contraceptive methods, the LN women are protected by the appearance of unplanned pregnancy, especially when SLE/LN is active, and the therapeutic regimen consists of teratogenic drugs (19).

All the patients can receive intrauterine devices, in the absence of gynaecological complications. Petri et al. and Sánchez-Guerrero et al. demonstrated in their studies the benefits of combined hormonal pills (oestrogen plus progestin) or only progestin pills in inactive or active, but stable SLE/LN, in the absence of antiphospholipid syndrome (41,42).

Presence of antiphospholipid antibodies contraindicates the hormonal pills use, because of in-

creased risk of thrombotic events. If the patients are treated with anticoagulant drugs, these pills will be permitted (19).

New onset SLE during pregnancy

New onset of SLE during pregnancy or postpartum period is a rare event, with an incidence between 1 and 13.5% (43). It tends to occur during the first and second trimesters, and the more common features are LN, and severe thrombocytopenia (1). Renal involvement in new onset of SLE during pregnancy is different reported by the several authors: 68.8% of cases (44), 56.1% of patients (45), 47% of cases (46), 94.7% of cases (47).

First onset of LN during pregnancy is marked by severe proteinuria, haematuria and even nephrotic syndrome. Zhao et al, showed in their study that LN developed during pregnancy presented higher level of proteinuria, significant reduction in the level of serum albumin and IgG. The incidence of nephrotic syndrome was significantly higher in the new onset LN during pregnancy than that in the nonpregnant patients (66.7% versus 34.8%, $p < 0.05$) (44). In another study, performed by Chen et al. the incidence of nephrotic syndrome, as a expression of LN, was approximately of 73.6% cases (47).

New diagnosis of LN during pregnancy is associated with worse outcomes both for the mother and the fetus, being represented by: new-onset hypertension, preeclampsia/eclampsia and HELLP syndrome, even maternal death due to severe organ failure, and fetal loss, spontaneous abortion, preterm birth. The onset of SLE in the third trimester has a better prognosis, favoring live term deliveries (1,25).

CONCLUSIONS

1. The pregnancy is a challenging problem in patients with SLE and LN.
2. Pregnant female patients with SLE and LN are considered at "high risk" and must be rigorously monitored.
3. In female patients with SLE and LN the planification of pregnancy is mandatory for a good result for mother and child.
4. The knowledge of drugs accepted or contraindicated in pregnant female with SLE and LN is very important
5. New onset of SLE and even LN during pregnancy is a rare event, but sometimes associated with worse results for mother and foetus

6. The cooperation between various specialists (rheumatologist, nephrologist, obstetrician) is

very important for a good maternal and fetal outcome.

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