ISSN: 2837-4614

Archives of Reproductive & Medicine

DOI: 10.33552/ARM.2022.01.000502

Iris Publishers

Research Article

Lupus Nephritis in Pregnant Women, Literature Review

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Received Date: May 09, 2022

Published Date: June 02, 2022

Introduction

Systemic Lupus Erythematosus is a multi-organ disease that manifests itself in approximately sixty-five percent of patients who are between 16 and 55 years of age at the time of onset of the pathology, mainly affecting women of childbearing age [1,2]. Although its etiology is not very well defined, multifactorial events can explain the origin of this, mainly attributed to the estrogenic hormonal effects that influence the incidence and severity of said pathology [3], environmental factors, factors linked to mutations in the X chromosome [4] and certain sociodemographic characteristics are relevant in the epigenetic complex, studies have highlighted that African Americans and Mexican Hispanics have a worse renal prognosis [5] which can end in a lupus nephritis -resistant to therapeutic schemes such as cyclophosphamide- with respect to the Caucasian population at [6]. Women with lupus, particularly lupus nephritis, may have an increased risk of obstetric and fetal problems during pregnancy, as well as problems related to the disease. However, the prospects for pregnancies in this context have improved significantly and success rates of more than 90% can be achieved thanks to advances that allowed a better understanding of the disease and the simultaneous interdisciplinary provision of specialists [7].

Pregnancy as an Altered Immune State and its Relationship with Systemic Lupus Erythematosus

Gestation is characterized by hormonal modulation of immunity and its types to establish maternal tolerance to a somatogenic fetus that expresses both antigens from its parents. Normally, the number of CD41/CD251 regulatory T cells [Tregs] increases, whose function is to act as immunosuppressants and contribute to fetal tolerance. In addition, normal pregnancy is characterized by a shift from a Th1 cell-mediated immune response to a Th2 antibody-mediated one. However, TH2 cell polarization does not occur with pregnancy progression in women with SLE, as much as it does in healthy pregnant women [8,7].

In pregnancies of women suffering from SLE compared to pregnancies in healthy women, the serum level of multiple pro-inflammatory cytokines is higher – such as interleukin [IL] – 6, IL-10, IL-17, and TNF. In the same comparative scenario, regulatory T cells are another important group of immunological agents that become defective and are present in smaller numbers [9].

A study by [Andrade, et al.] recognized a new mechanism through which IFN-α induces an antiangiogenic medium, increasing

the sensitivity of endothelial cells to soluble vascular endothelial growth factor [VEGF], also known as FMS-like tyrosine kinase. 1 [sFlt1] and suggests that increased IFN-α could also contribute to the pathogenesis of preeclampsia in some pregnancies with SLE [10] (Figure 1).

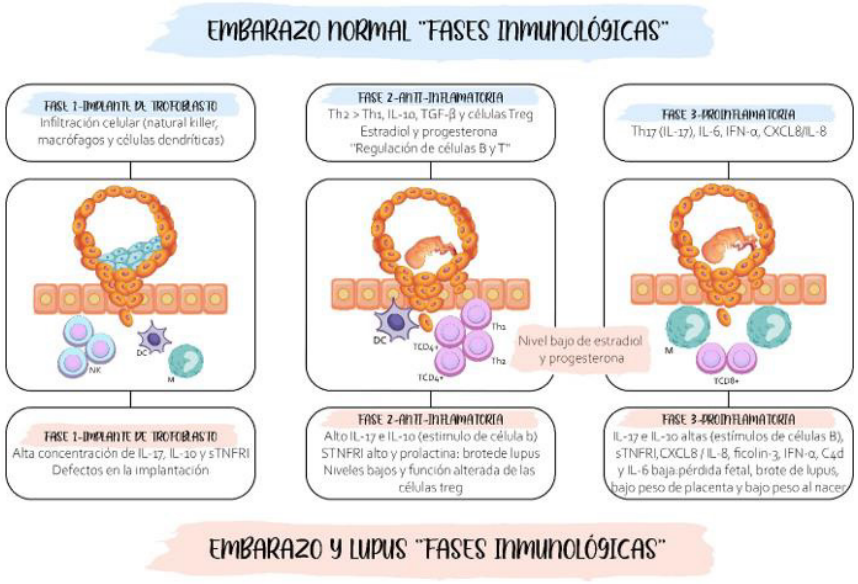

Figure 1: Immunological phases in normal pregnancies and with SLE.

Physiological Renal Changes and Lupus Nephritis

Women during pregnancy are predisposed to suffer from symptomatic pyelonephritis and urolithiasis due to hormonal stimuli by progesterone that causes relaxation of the smooth muscle and by the compression of the ureters by the increase in size of the uterus that led to physiological hydronephrosis. Another change can be observed in the approximately 50-60% increase in Glomerular Filtration Rate [GFT] associated with a subsequent creatinine elevation of 30%. Serum creatinine varies according to the time of gestation and is found in a lower proportion in pregnant women than in those who are not. Serum creatinine values of 0.9 mg/dl [11, 12]. have been taken as an indicator of pre-existing kidney damage that may be accompanied by elevated proteinuria or worsening of arterial hypertension, so they must be differentiated from whether they are de Novo, exacerbation of lupus nephritis or preeclampsia even in its severe form, HELLP syndrome. [13] Lupica Nephritis is one of the findings that most often induces high morbidity and mortality during pregnancy. Patients with Lupica nephritis more frequently use high doses of corticosteroids and immunosuppressive agents, which predisposes to a higher frequency of serious infections and hospitalizations [14].

The precise characterization of the outbreak of lupus nephritis is one of the most complicated and difficult aspects of the pregnancy of a woman with lupus and, therefore, the differentiation of PD. Medical diagnosis is critical because treatment varies significantly: in PD childbirth should be considered, while immunosuppressive medication should be administered to patients with systemic erythematous lupus nephritis. However, distinguishing the two can be challenging because lupus nephritis increases the risk of preeclampsia [15] (Table 1).

Table 1: Differentiation of preeclampsia, HELLP syndrome and active lupus nephritis.

	Pre-Eclampsia	Syndrome Help	Active Lupus Erythritis
Timing of pregnancy	After the week 20 gestation	After the 20th week of pregnancy	The whole gestation
Complement (c3, c4)	Normal	Normal	Normally decreased
Thrombocytopenia	Absent	Present	Present
Neutropenia	Absent	Absent	Present
Urinary Sediment Active	Absent	Absent	Present (may be benign in the membranous nephritis)
Participation of others Body	Absent	Absent	Present
Anti-DNA antibodies double stranded	Absent	Absent	Present

Anti-c1q antibodies	Normal	Normal	It can be high
Function tests abnormal liver function	Absent	Present	Absent
Uric acid in serum	Increase	Increase	Normal (Can be elevated with FG reduced)
Hypertension (>140/90mmHg	Present	Absent in 10-15%	Variable
Increase in creatinine (>1.2 mg/dL)	Usually, absent	It can occur in up to 10%	Commonly present

Preconception, Risk Assessment and Prenatal Assessment

Fertility should be considered at all times and lupus does not alter it, but the prolonged use of drugs such as cyclophosphamide can have a negative effect on it, as well as the progression of renal injury. It is necessary to analyze the age, how long the woman has been wishing to conceive and if this is the case to investigate simultaneously the time of use of cyclophosphamide and the degree of renal dysfunction [16].

Lupus should be inactive for at least 6 months prior to the desire to conceive, especially if you have active lupus nephritis. This recommendation should be informed to the patient if she suffers from a lupus flare-up that requires increased treatment. For women with lupus nephritis, it is safer to wait about 12 months because the average time for remission is around 9 months and then logically requires a therapeutic switch to a non-teratogenic drug [17, 18].

Factors Associated with an Increased Risk of SLE Outbreak During Pregnancy

Pregnant women with SLE are not exempt from an outbreak of the disease, however studies affirm a strong trend during the third trimester. Because the timing of flare-ups is unpredictable, regular follow-up during gestation and postpartum is indicated. A Doria, A Tincani, M Lockshin, (2008) "Challenges of lupus pregnancies," Rheumatology, vol. (47) supplement 3, pp. iii9–iii12 (Figure 2).

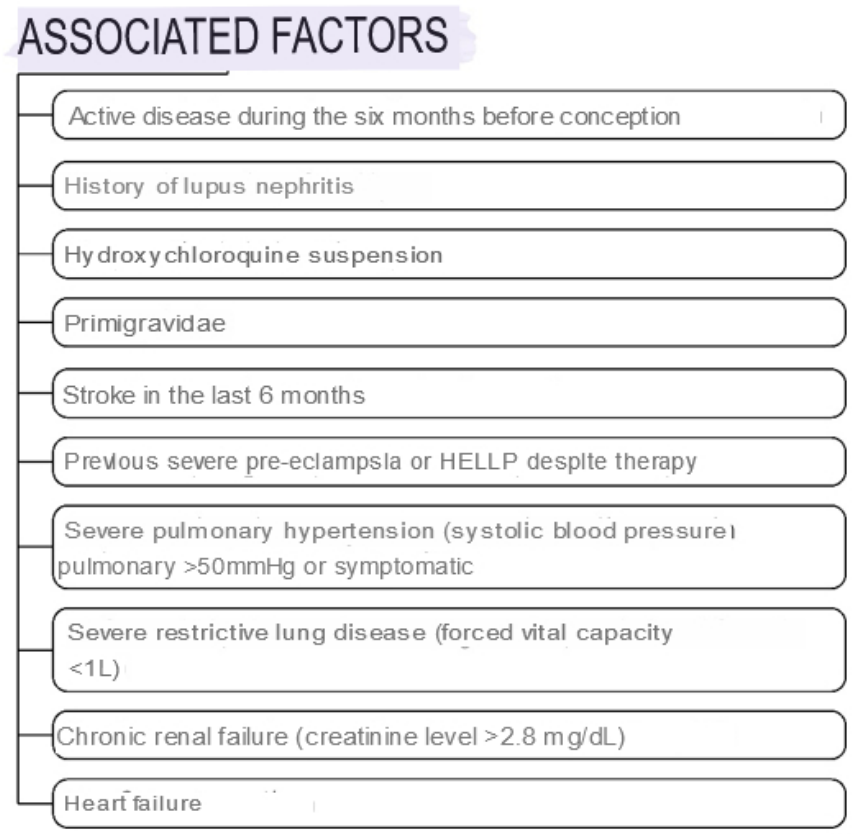

Figure 2:

If during pregnancy, there is a mismanagement of the disease this is reflected in harmful damage to the results of pregnancy. As mentioned above, studies show a high rate of pregnancy loss when the disease is active within at least 6 months prior to conception [19], as well as hypocomplementemia or anti-dsDNA positive that is additionally associated with preterm delivery [20] Therefore, the woman should be constantly monitored during preconception, pregnancy and postpartum.

A study conducted in the United States of America showed how patients with SLE versus those who do not suffer from this disease, have a 4 times greater probability of suffering from a complication such as pregestational diabetes mellitus [21].

Prenatal treatment of pregnant patients with systemic lupus erythematosus needs a comprehensive evaluation among specialists – monthly if there are outbreaks of the disease. Monitoring should be more frequent and thorough than standard antenatal care. Each visit should include an intensive physical examination, routine monthly laboratory tests [complete blood count, measurement of serum uric acid, urea, creatinine and electrolyte levels, liver function tests, urinalysis, analysis of urine samples to determine protein relationship: creatinine, evaluation of complement levels and ds DNA antibodies] and specific investigations, adapted to the risk profile. It is important to note that prior to conception serial studies should be carried out to evaluate the activity of the disease and the affection of important organs, also as hypercoagulability or medical disorders that affect pregnancy.

Previous obstetric outcomes should be reviewed, paying particular attention to the history of fetuses small for gestational age, preeclampsia, stillbirth, miscarriage, and preterm birth [22]. It is recommended according to specialists to perform weekly prenatal check-ups until week 28 then every two weeks until the beginning of week 36 and finally it is repeated every week. It is imperative to carry out a routine control of blood pressure figures to detect early hypertension either due to pregnancy or for any complication.

A complete set of relevant antibody profiles should be obtained at the preconception visit. These should include aFL [anticardiolipin and lupus anticoagulant antibodies] and anti-Ro and anti-La antibodies. Disseminated lupus erythematosus activity and organ functioning should be assessed to help with whether to continue the pregnancy, in addition to assessing the risk of pregnancy. Thyroid function should be monitored, as thyroid disease is understood to have an adverse effect on pregnancy outcomes [23].

Antiphospholipid antibodies [aFL] are present in about a quarter to half of SLE patients. Some of these are asymptomatic while others develop thrombotic and obstetric complications typical of antiphospholipid syndrome [APS] that is defined by the persistence of medium to high titer levels of aFL in at least two laboratory tests, separated by an interval of 12 weeks and presenting at least one clinical criterion of thrombosis or morbidity of pregnancy [24]. Treatment in these cases will depend on the underlying morbidity and mortality factors and it is common to profile these pregnant women in 3 subgroups of asymptomatic carriers, obstetric FAS, and FAS with systemic thrombosis. They should usually perform fetal well-being tests such as a non-stress test and a fetal biophysical profile during the third trimester in conjunction with a therapeutic regimen of antiplatelet agents and anticoagulants, can prevent maternal-fetal complications [25].

Neonatal lupus syndromes. NLS are a form of fetal autoimmunity passively acquired from maternal antibodies, anti-Ro and anti-La antibodies, cardiac complications are the result of permanent damage to the fetal cardiac conduction system by maternal antibodies. Cardiac manifestations of NLS include conduction defects, structural abnormalities, cardiomyopathy, and congestive heart failure. The most common complication in these patients is congenital heart block, which has fetal mortality rates with values between 15%-30%. It is suggested that the risk of congenital heart block is higher in anti-Ro positive women with hypothyroidism, compared to women with normal thyroid function. [26] Most survivors require pacemakers; however, congenital heart block affects approximately 2% of children born to primigravid women with anti-Ro antibodies [27] (Figure 3).

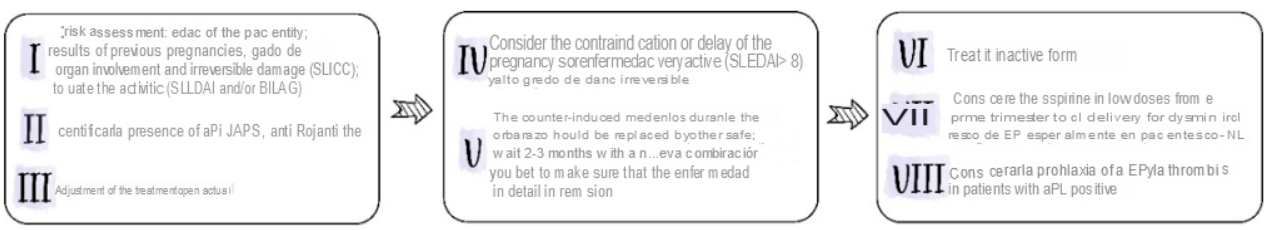

Figure 3: Pregnancy Planification for Lupus Patients.

Pharmacotherapy During Pregnancy

It is essential to discuss the use of pharmacological therapeutic measures that may mean a possible toxicity that cause either the conclusion of the necessary therapy or a resulting increase in the

activity of the disease. Therefore, the challenge of specialists is to choose the right drugs that do not simultaneously compromise the life of the mother and the baby.

Corticosteroids

Corticosteroids of the prednisone and prednisolone type are the treatment of choice in cases of outbreaks of Systemic Lupus Erythematosus during pregnancy. These are inactivated by enzymatic processes thanks to the 11-β-hydroxysteroid dehydrogenase 2 that reduces fetal exposure with respect to the maternal dose [28]. Doses between 5-10 mg/d are recommended and are unlikely to cause complications such as adrenal insufficiency and thymic hyperplasia however a strong association has been seen between dyslipidemia, arterial hypertension, fluid retention and hyperglycemia and doses above 10 mg/d however intravenous pulses of methylprednisolone can be used safely if indicated in severity of the disease [29,30]. Corticosteroids do not enter breast milk in massive amounts and there are no contraindications to breastfeeding in women who are being treated with corticosteroids.

Aines

It was previously considered safe to use nonsteroidal anti-inflammatory drugs during the first and second trimesters [31,32], however, birth defects have been associated due to the use of NSAIDs in the first trimester and impaired renal function after the 20th week of gestation that may promote the development of oligohydramnios [33]. Very cautious should be exercised with the use of NSAIDs during early stages of pregnancy as well as after week 32 due to the elevated risk of premature closure of the ductus arteriosus [34].

Hydroxychloroquine

Hydroxychloroquine should be continued during pregnancy in all patients. Therapeutic discontinuation causes an increase in outbreaks of the disease. Thanks to its use in a cohort study and a randomized controlled test, an attenuated activity of the disease and whether no adverse effects or congenital malformations were evidenced [35,36]. A multidisciplinary professional panel has advocated for its use as a frontline in pregnancies complicated by NL [37].

Azathioprine

Azathioprine in doses of up to 2.0 mg/ kg/day, is one of the pharmacological therapies par excellences used in SLE outbreaks during pregnancy, being the immunosuppressant of choice for the treatment of severe maternal disease or refractory to the isolated use of corticosteroids. It is compatible with breastfeeding being safe for the fetus [38] (Table 2).

Table 2: Pharmacotherapy pregnant with SLE.

Medicine	Allow	Contraindicated
Steroids	Prednisolone, methylprednisolone in pulse Betamethasone, Dexamethasone	NA
Antimalarials	Hydroxychloroquine	NA
Immunosuppressants	Azathioprine, Cyclosporine, Tacrolimus	Cyclophosphamide, Mycophenolate mofetil, Methotrexate, leflunomide, Rituximab, Belimumab
Antiplatelet Agents	Aspirin	Ticlopidine, Clopidogrel
Anticoagulants	Heparin	Warfarin
Antihypertensive	Methyldopa, Labetalol, Nifedipine, Hydralazine (with caution), Beta-blocking agents-adrenergic (with caution),	ACE inhibitors, ARB Diuretic
Analgesics and in flam mattery	Paracetamol NSAID (up to week 32)	Cyclooxygenase 2 inhibitors
Treatments to prevent osteoporosis	Calcium supplements vitamin D	Bisphosphonates
Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin in receptor blocker; NA, not applicable		

Special Therapeutic Considerations

- 6 months prior to conception most immunosuppressive drugs such as Cyclophosphamide, methotrexate, mycophenolic acid should be discontinued and for no reason should they be used as therapeutic measures during pregnancy [39].
- Those women who present hypertensive disorders as a consequence of the complications of the disease, most antihypertensive drugs are contraindicated and are associated with multisystem failures and even death, Therefore, treatment is limited to drugs such as methyldopa, hydralazine and labetalol [40-42].
- Vitamin D and calcium are used as alternatives to the use of bisphosphonates – which are so contraindicated in pregnancy – especially in pregnant women with long-standing corticosteroid schemes [43] (Table 3).

Table 3: Immunosuppressive drugs in pregnant women with SLE.

Medicine Acceptable in Pregnancy	Adverse Effects	Recommendation on Almaraz	Recommendation in Lactation
Azathioprine	Case reports include babies small for gestational age hematological toxicities and immunosuppression	Low risk at low doses (<2 mg/kg/g)	Compatible at lose doses (<2 mg/kgd)
Calcineurin inhibitors (tacrolimus and cyclosporine)	Hypertension gestational diabetes	Low risk. Monitor drug levels therapeutic	compatible
Hydroxychloroquine	Abstinence during pregnancy it can cause an outbreak	Low risk	compatible
Glucocorticoids	Gestational diabetes Premature rupture of membranes Cleft lip and palate T	Low risk. Use the minimum effective dose during the pregnancy	compatible
Avoid in pregnancy			
Cydophosphamide	Teratogenicity Pregnancy loo Myelosuppression	Contraindicated, discontinue at least 12 months before pregnancy	Contraindicated
Leflunomide	Teratogenicity	Contraindicated, discontinue at least 2 years before symptoms of pregnancy	No data
Methotrexate	Teratogenicity Pregnancy loss	Contraindicated, discontinue at least 1-month before symptoms of pregnancy	Contraindicated
Mycophenolate mofetil Teratogenicity Miscarriage Contraindicated, discontinue at least 6 weeks before Pregnancy			No data
Rituximab	Neonate B cell depletion	Limited data. Avoid during pregnancy a unless the potential benefits outweigh the risk; discontinue at least 12 months prior to the conception	Avoid breast feeding for at least 6 months after stopping rituximab
*The Food and Drug Administration no longer supports the use of pregnancy risk categories. The breast-feeding labeling rule during pregnancy requires that the label of the product specifically summarize the risk, clinical considerations and for each drug			
In some reports, with exposure during the first ester; the association has not been confirmed in population studies			

Diagnosis by Biopsy, Safe in Pregnant Women

Glomerular, tubule-interstitial and vascular lesions are the cause of renal impairment and its function [44]. Lupus nephritis occurs in about 40% of patients in a period of time after 5 years [45] of having diagnosed the disease and may lead to end-stage renal disease [46], however thanks to the better pathophysiological understanding of the disease and the ability of the clinician to make diagnoses in early stages, the presentation became mild with a marked decrease in progressive diseases that were part of the possible complications [47].The 5-year survival rate of patients with lupus nephritis was 44% prior to the introduction of glucocorticoids, which together with immunosuppressants improved in the 80s by 80% to 5 years and more than 90% in the current period [47-49].

Renal biopsy is the diagnostic test par excellence in the evaluation and treatment of lupus nephritis, due to lack of an unequivocal correlation between manifestations and histological alterations [50,51]; which are used for differentiation into pathological classes and define the severity of renal involvement not only of active or chronic lesions but also of diseases not related to lupus nephritis such as IgA nephropathy, thrombotic microangiopathies, drug-induced tubulointerstitial nephritis, diabetes nephropathy, or hypertensive nephroangiosclerosis [52].

To perform invasive investigations such as renal biopsy, the level of 500 mg/24 ho the urinary point protein/creatinine ratio [UPCR] > 500 mg/g [50 mg/mmol] is taken as a reference, especially with impaired renal function or active urinary sediment [53,54]. Similarly, it can be considered in the presence of pictures with persistent hematuria or pyuria after having ruled out other causes, or in cases of unexplained renal failure with normal urinalysis [55,56].

Histological classes are divided into 6 and obeying microscopic lesions and the distribution of immune complexes [CI] [57]. Lupus nephritis [NL] of class I -minimum mesangial- represents less than 20% of the cases that undergo biopsy and has a prevalence of 1% in adults [58,59]. Class II NL -mesangial proliferative- is usually represented with hematuria, low-grade proteinuria and normal renal function, in addition, it appears between 7-22% of cases [60-62], it is considered mild although it is associated with the risk of a progression to focal or diffuse NL [63,64]. More severe prognoses with the need for immediate immunosuppressive treatment are observed in class III and IV LN -focal and diffuse NL. The most prevalent and with the highest risk of progression to end-stage renal disease was class IV according to a meta-analysis that assessed the prevalence found by biopsy [55], many of these patients do not reach remission and those who achieve it have relapses

between 15-30% of cases. Class V -membranous- is characterized by immunocomplex deposits in the subepitile mainly, with a loss of pudicities. Pure class V presents clinically with nephrotic or non-nephrotic proteinuria and normal or only slightly elevated serum creatinine [65]. Class VI -advanced sclerosing- [globally glomeruli sclerosed without residual activity] is defined by> 90% of the sclerotic glomeruli that result in impaired renal function. It is important to clarify that over the years there has been an increase in mixed forms of presentation [III+IV and IV+V] reflecting the process of updating the classification [47] (Figure 4).

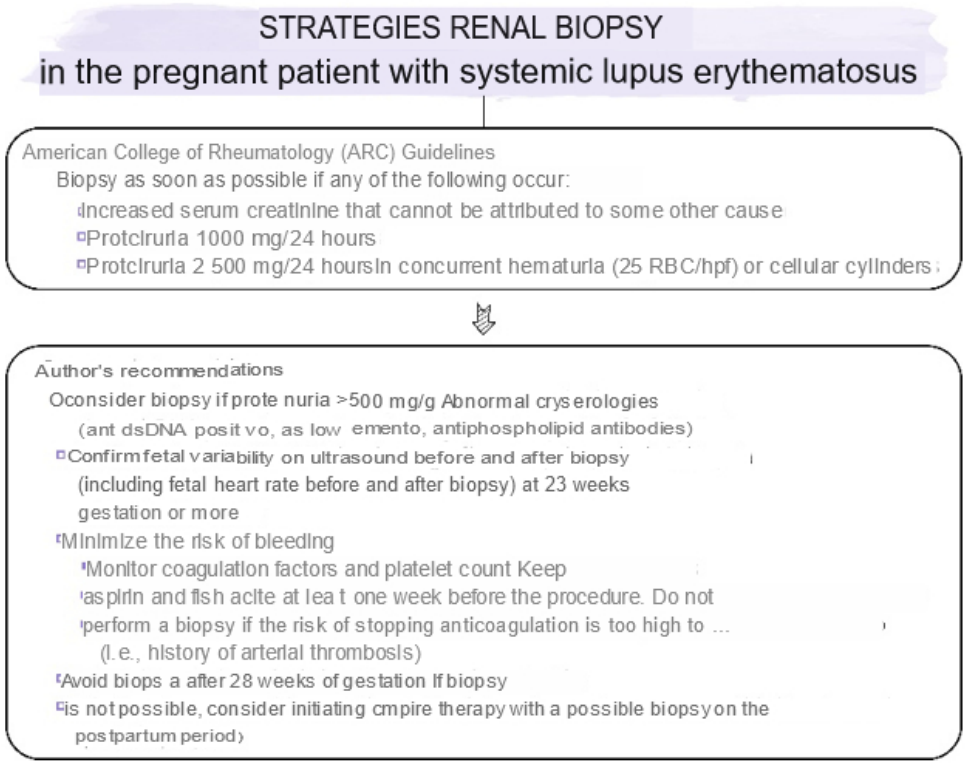

Figure 4: Renal biopsy strategies in the pregnant patient with systemic lupus erythematosus.

As described above, gestation is a state that must be properly planned under the therapeutic considerations mentioned especially rigorously in those pregnant patients or with a desire to have a baby with lupus nephritis, which is why the use or not of biopsy is a controversial issue for specialists because it could mean risks such as bleeding, infection, compromise of placental blood flow and should be considered how these risks could affect not only the mother but also the fetus. On the other hand, the benefits of performing a biopsy are the definitive diagnosis, the best therapeutic option and a possible prolongation of pregnancy. Depending on the gestational age at the time of onset of lupus nephritis, pregnancy may be prolonged to reduce the neonatal morbidity that accompanies prematurity.

A 2015 case series study using a pathology database at Johns Hopkins Hospital examined all biopsies to identify lupus patients who underwent a kidney biopsy during pregnancy reported results after kidney biopsy in 11 pregnant women with SLE. A large number of patients – proportion 9 of 11 – prior to the biopsy had no history of lupus nephritis, another important fact is that 10 of 11 pregnant women included in the study had to make a change in their therapeutic management either termination of pregnancy or the inclusion of immunosuppressive therapy, in general there were no major complications associated with the taking of the biopsy, thus supporting the use of renal biopsy during pregnancy when the information obtained serves to establish the definitive diagnosis and its respective therapy. Gestational age at the time of clinical decision-making is a crucial consideration to perform or not a renal biopsy, within the first trimester is associated with a low risk, however, at the end of pregnancy it is advisable to postpone the biopsy until after delivery, unless there are considerations for early delivery as it is in the case of a serious disease, however, with or without the need for biopsy, appropriate treatment early is necessary [66].

Contraceptive Measures

The progestin tablet alone and the intrauterine contraceptive device [IUD] showed similar efficacy and safety to oral

contraceptives62. Bone mineral density results.63 For many SLE patients, an IUD is probably the best birth control option [67,68].

Postnatal Care

The four weeks postpartum require a clinical assessment, especially in those pregnant women with recent activity or serious illness due to the high risk of thrombo-embolic complications and that in some cases when they present aFL antibodies a prophylaxis is recommended at least 4-6 weeks after delivery [69,70].

Acknowledgement

None.

Conflict of Interest

No conflict of interest.

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