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MESTRADO INTEGRADO EM MEDICINA

Systemic Lupus Erythematosus and Pregnancy: A retrospective single-center study

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M

2024

Systemic Lupus Erythematosus and Pregnancy: A retrospective single-center study

Dissertação de candidatura ao grau de Mestre em Medicina, submetida ao Instituto de Ciências Biomédicas Abel Salazar – Universidade do Porto

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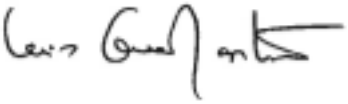

Porto, maio de 2024

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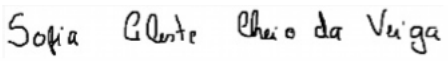

28 de Maio de 2024

Acknowledgements

Completing this thesis would not have been possible without the collaboration and support of numerous individuals, and I am thankful for their support. First and foremost, I would like to express my sincere appreciation to Professor António Braga, my supervisor, and Professor Luís Guedes, my co-supervisor, for their invaluable guidance throughout the entire process of this dissertation.

I would also like to give special recognition to my family and friends, who have given me plenty of support. Their unconditional love, dedication, and efforts have provided me with the necessary tools to succeed in the future.

Resumo

Introdução: Lúpus Eritematoso Sistémico é uma doença autoimune multissistémica com uma ampla apresentação, progressão e prognóstico, frequentemente associada a alta morbilidade e mortalidade. A gravidez é possível em mulheres com esta doença. No entanto, está associada a uma maior taxa de eventos adversos na gravidez.

Objetivo: Avaliar o impacto do Lúpus Eritematoso Sistémico na fertilidade, nos *outcomes* da gravidez e na progressão da doença, e identificar os fatores de risco associados a eventos adversos e fatores protetores, numa coorte de doentes.

Métodos: Foi realizada uma revisão retrospetiva de todas as grávidas com Lúpus Eritematoso Sistémico seguidas no hospital terciário, Centro Hospitalar Universitário de Santo António (CHUdSA), de 1993 a 2023. Novos dados obstétricos e ginecológicos sobre os *outcomes* da gravidez foram obtidos, através da revisão de registos médicos. Informações demográficas maternas foram registadas e os *outcomes* materno-fetais e neonatais foram avaliados. A atividade da doença antes e durante a gravidez foi avaliada. Foi realizada uma análise multivariada.

Resultados: Foram incluídas 266 gestações de 173 pacientes. A síndrome antifosfolipídico estava presente em 23,8% e a nefrite lúpica em 17,8% das mulheres. A atividade da doença estava baixa ou ausente em 92,9% das pacientes no momento da conceção. Durante a gestação, 80,1% das pacientes estavam sob tratamento, sendo a hidroxicloroquina o fármaco de preferência, correspondendo a 67,3%. O ácido acetilsalicílico em baixas doses foi prescrito na conceção em 88,7% dos casos. A taxa de nados vivos foi de 86,7%. *Outcomes* adversos na gravidez ocorreram em 36,1% das gestações. Foi verificada uma taxa de aborto espontâneo de 14,3% e uma taxa de parto prematuro de 15,2%. A pré-eclâmpsia complicou 10,5% e a restrição do crescimento fetal 14,6% das gestações. O lúpus neonatal ocorreu em 5,8% dos recém-nascidos e houve dois casos de bloqueio cardíaco congénito. Fatores de risco significativos para os *outcomes* adversos na gravidez foram a atividade da doença na conceção, hipocomplementemia, positividade para anticoagulante lúpico, síndrome antifosfolipídico e *flare* lúpico. O uso de ácido acetilsalicílico foi significativamente associado a uma redução na incidência de aborto espontâneo. Um *flare* de lúpus foi diagnosticado em 15,3% dos casos. Os fatores de risco para *flares* foram história prévia de nefrite lúpica, presença de doença ativa na conceção e uso de medicação crónica.

Conclusão: O*utcomes* adversos da gravidez, nomeadamente aborto, parto pré-termo, doenças hipertensivas e restrição de crescimento, estão estatisticamente associados ao Lúpus eritematoso sistémico.

Palavras-chave: Gravidez, lúpus eritematoso sistémico, síndrome antifosfolipídico, lúpus renal, hidroxicloroquina.

Abstract

Introduction: Systemic Lupus Erythematosus is a multisystemic autoimmune disease with wide-ranging presentation, progression, and prognosis, often associated with high morbidity and mortality. Pregnancy is possible in women with this disease. However, it is associated with a higher rate of adverse pregnancy outcomes.

Objective: Study the impact of Systemic Lupus Erythematosus on fertility, pregnancy outcomes, and disease progression, and to identify risk factors associated with poor outcomes and protective factors, in a cohort of patients.

Methods: We conducted a retrospective study comprising all pregnant patients with Systemic Lupus Erythematosus, followed in the tertiary hospital, Centro Hospitalar Universitário de Santo António (CHUdSA) from 1993 through 2023. New obstetric and gynaecological data on pregnancy outcomes was obtained, by reviewing medical records. Baseline maternal information was collected, and maternal–fetal and neonatal outcomes were evaluated. Disease activity before and during pregnancy was assessed. A multivariate analysis was used.

Results: We included 266 pregnancies from 173 patients. Antiphospholipid syndrome was present in 23.8% and Lupus nephritis in 17.8% of the women. Disease activity at conception was low or absent in 92.9% of the patients. During gestation, 80.1% of the patients were under treatment, and hydroxychloroquine was the preferred drug, 67.3%. Low-dose acetylsalicylic acid was prescribed at conception in 88.7% of the cases. The live birth rate was 86.7%. An adverse pregnancy outcome occurred in 36.1% of the pregnancies. A miscarriage rate of 14.3% and a preterm delivery rate of 15.2% were observed. Preeclampsia was present in 10.5% and fetal growth restriction in 14.6% of the gestations. Neonatal lupus occurred in 5.8% of the newborns, and there were two cases of congenital heart block. Significant risk factors for adverse pregnancy outcomes were disease activity at conception, hypocomplementemia, positivity for lupus anticoagulant, antiphospholipid syndrome and lupus flare. The use of acetylsalicylic acid was significantly associated with a reduced incidence of miscarriage. A Lupus flare was diagnosed in 15.3% of the cases. Risk factors for lupus flares were a previous history of lupus nephritis, the presence of active disease at conception, and the use of chronic medication.

Conclusion: Adverse Pregnancy outcomes, particularly miscarriage, preterm delivery, hypertensive diseases and fetal growth restriction, are statistically linked with Systemic Lupus disease.

Keywords: Pregnancy, systemic lupus erythematosus, antiphospholipid syndrome, renal lupus, hydroxychloroquine.

Abbreviations

aB2GPI - anti-β2 Glycoprotein

aCL- anti-Cardiolipin

ACOG- American College of Obstetricians and Gynecologists

ANA - Antinuclear Antibodies

APO- Adverse Pregnancy Outcome

APS - Antiphospholipid Syndrome

ASA – Acetylsalicylic Acid

AZA- Azathioprine

CHB - Congenital Heart Block

CHUdSA – Centro Hospitalar Universitário de Santo António

dsDNA - double-stranded Deoxyribonucleic Acid

EULAR - European League Against Rheumatism/American College of Rheumatology

FGR- Fetal Growth Restriction

GD- Gestational Diabetes

HELLP- Hemolysis Elevated Liver enzymes and Low Platelets

HCQ - Hydroxychloroquine

HDP - Hypertensive Disorders of Pregnancy

LAC - Lupus Anticoagulant Test

LMWH – Low Molecular Weight Heparin

NICU - Neonatal Intense Care Unit

OGTT- Oral glucose tolerance test

PE- Preeclampsia

PTD - Preterm Delivery

SD – Standard Deviation

SLE - Systemic Lupus Erythematosus

SLEDAI - Systemic Lupus Erythematosus Disease Activity Index

SLEPDAI - Systemic Lupus Erythematosus Pregnancy Disease Activity Index

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Introduction

Systemic lupus erythematosus (SLE) is a multisystemic autoimmune disease with wide-ranging presentation, progression, and prognosis, often associated with high morbidity and mortality.[1,2] Although the exact cause of SLE remains unknown, various immunopathogenic pathways have been linked to its development and progression.[2]

According to recent studies, the global incidence of SLE is estimated to be 5.14 per 100,000 person-years, with a higher prevalence in women of reproductive age, demonstrating a female-to-male ratio of 9:1.[3,4] Furthermore, it is also believed that SLE can impact fertility and fecundity due to chronic inflammation, which can lead to auto-oophoritis, dysfunction of the hypothalamic-pituitary-ovarian axis, and abnormal uterine bleeding, resulting in menstrual irregularities and premature ovarian failure.[5]

However, with the advancements in treatment and the improvement of patient monitoring, the consequences of SLE on pregnancy have been significantly reduced, allowing for successful pregnancies in numerous cases.[6,7] Nonetheless, in comparison with healthy women, those with this disease are at greater risk for adverse obstetric outcomes such as miscarriage, stillbirth, preterm delivery, growth restriction, preeclampsia, and other hypertensive disorders. [6,8,9]

Additionally, pregnancy can influence the course of SLE, with an increased likelihood of flares in pregnant women up to 70%, when compared to non-pregnant individuals, depending on the level of disease activity six months before conception and the presence of renal disease. [4,6,9-11] Therefore, control of the disease prior to conception is crucial to obtain a favourable outcome. Pregnancy should be discouraged if severe organ damage is present, including severe pulmonary hypertension (above 50 mmHg or if symptomatic), a restrictive pulmonary disease with a functional residual capacity inferior to 1L, cardiac or renal failure, and a severe flare, jaundice, or stroke occurring in the last six months. [2,6-12]

This thesis aims to study the impact of SLE on fertility, pregnancy outcomes, and disease progression, with an emphasis on identifying risk factors associated with poor outcomes and protective factors to develop effective management strategies for pregnant women with SLE.

Materials and Methods

We conducted a retrospective study comprising all pregnant patients with SLE, followed in the tertiary hospital, Centro Hospitalar Universitário de Santo António (CHUdSA) from 1993 through 2023. New obstetric and gynaecological data on pregnancy outcomes was obtained, by reviewing medical records. The study was approved by the Ethical Committee of Santo António, with the process number 2023.277(238-DEFI/229/CE).

Patients

The inclusion criteria for this study were pregnant women with SLE who were managed at the Obstetrics Department and Immunology Clinical Unit of the tertiary hospital, Centro Hospitalar Universitário de Santo António (CHUdSA), between January 1993 and 2023, consisting of a total of 173 patients. The study included both natural and medically assisted pregnancies, each pregnancy being considered individually. The patients met the 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for Systemic Lupus Erythematosus.[1, 13, 14.]

Baseline maternal data consisted of age, past obstetric history, duration of SLE, previous and current symptoms of SLE, active disease in the previous six months, prior diagnosis of antiphospholipid syndrome, arterial hypertension, diabetes mellitus, and medications. Active disease in the six months prior to conception was assessed using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI). A SLEDAI of 0 indicates remission, if the index is between 1 and 4, it corresponds to low activity, 5 to 10 is considered moderate activity, and if superior to 10, high activity. [13,15]

During pregnancy, the Systemic Lupus Erythematosus Pregnancy Disease Activity Index (SLEPDAI) was used to assess the activity of the disease.[16]

Periconceptional laboratory testing was performed: Complete blood count and liver function test. Renal function was evaluated by serum levels of creatinine, urinalysis with urine sediment, and spot urine protein/creatinine ratio. An immunological evaluation was also required: antinuclear antibodies (ANA), anti-double-stranded deoxyribonucleic acid (dsDNA) antibodies, anti-Ro/SS-A and anti-La/ SS-B, anti-cardiolipin (aCL), and anti-β2 glycoprotein (aB2GPI) antibodies, lupus anticoagulant test (LAC), and c3 and c4 complement components.

Internal Medicine and Obstetrics Management Protocol

The institutional protocol used to evaluate all patients was designed for pregnant women with SLE and based on EULAR recommendations. This protocol included specifications for the frequency of medical appointments, required exams, fetal growth and vitality evaluation, and recommendations for delivery and postpartum care. It is mandatory to have a preconception consultation and plan pregnancy after six months of disease remission.

Pregnancy follow-up aims to detect complications of SLE, flares, and other pregnancy-related disorders such as hypertensive disorders of pregnancy (HDP), gestational diabetes (GD), fetal growth restriction (FGR), and congenital heart block (CHB). In these consultations, it is also assessed the risk of spontaneous preterm birth.

Chemical, haematological, and immunological parameters are monitored regularly and fetal sonographic evaluation with Doppler and fetal echocardiography are conducted. If no contraindication is present, hydroxychloroquine is introduced before conception, and, if not already prescribed, low-dose acetylsalicylic acid (ASA) is initiated once pregnancy is confirmed. Low-molecular-weight heparin (LMWH) is prescribed for patients with antiphospholipid syndrome (APS) or other risk factors for thromboembolic disease. If maternal or fetal complications are present, we advocate a low threshold for patient hospitalization and program delivery for termination of pregnancy at 39 weeks. All patients undergo re-evaluation in the early weeks of postpartum.

Assessment of SLE flares

The activity of SLE before conception was assessed using the SLEDAI score [13,15] over a period of six months, while the SLE activity during pregnancy was evaluated based on the SLEPDAI score[16] at the end of each trimester. In addition to the classification of severe flares in SLEPDAI, the need for new immunosuppressive medication during pregnancy or hospitalization due to SLE-related comorbidity was also considered.

Obstetric and fetal outcomes

Evaluations were made to determine maternal and fetal outcomes. Fetal outcomes were measured and included factors such as gestational age at delivery, birth weight, Apgar scores[17]

(newborn's health assessment at 1 and 5 minutes after birth), admission to the neonatal intensive care unit, the development of neonatal lupus or complete heart block (CHB), presence of congenital malformations, and respiratory distress syndrome.

It was defined as an adverse pregnancy outcome (APO), the occurrence of miscarriage, stillbirth, fetal growth restriction (FGR), preterm delivery (PTD), or the development of hypertensive disorders of pregnancy (HDP), such as gestational hypertension, pre-eclampsia, eclampsia and Hemolysis, Elevated Liver enzymes and Low Platelets (HELLP).

Spontaneous abortion was defined as the unexpected loss of a fetus before 20 weeks of gestation, stillbirth as the death of a fetus after 20 weeks of gestation, and elective abortion as the voluntary termination of pregnancy. PTD is the delivery before the 37th week of gestation.[7] FGR was defined according to the Portuguese population curves[18,] as a birth weight below the 10th percentile.

Preeclampsia was defined using the criteria of the American College of Obstetricians and Gynecologists (ACOG) in 2020[19] as the presence of systolic blood pressure higher or equal to 140 mmHg and/or diastolic blood pressure at higher or equal to 90 mmHg in at least two instances measured 4 hours apart, these findings must be present in previously normotensive women after 20 weeks of gestation and accompanied by new-onset proteinuria (≥30 mg/mol protein: creatinine ratio; ≥300 mg/24 hour; or ≥2 + dipstick) or uteroplacental dysfunction (fetal growth restriction, abnormal umbilical artery Doppler waveform analysis, or stillbirth) or evidence of other maternal organ dysfunction (acute kidney injury – creatinine ≥90 µmol/L; 1 mg/dL; liver involvement with or without abdominal pain - alanine aminotransferase or aspartate aminotransferase >40 IU/L; neurological complications - eclampsia, altered mental status, blindness, stroke, clonus, severe headaches, and persistent visual scotomata; or haematological complications - thrombocytopenia–platelet count <150 000/µL, disseminated intravascular coagulation, hemolysis).

Similarly, gestational hypertension was defined as systolic blood pressure of 140 mmHg or more or a diastolic blood pressure of 90 mmHg or more in two measurements at least 4 hours apart after 20 weeks of gestation, however without proteinuria and other organ dysfunction which returns to normal after childbirth.

In our study, the criteria for gestational diabetes (GD) diagnosis varied. Before 2011, the Carpenter and Coustan criteria[20] were used, and after 2011, the guidelines of the Portuguese Endocrinology Society were followed, which were adapted from the criteria of the International Association of Diabetes and Pregnancy Study Groups.[21,22.]

According to the previous criteria, gestational diabetes is diagnosed either in the first prenatal consultation if the fasting plasmatic glycemia value is between 92 and 126 mg/dl (5,1-7,0 mmol/l) or by an Oral glucose tolerance test (OGTT) between the 24 and 28 gestational weeks if the value of glycemia in the first evaluation is below 92 mg/dl. The OGTT is positive and diagnostic when fasting glycemia is above 126 mg/dl, is higher than 180 mg/dl one hour after ingestion of 75 grams of glucose, or if the value is between 153 and 199 mg/dl two hours after the glucose ingestion.

Statistical analysis

Descriptive data analysis was performed. The chi-square test compared categorical data between groups, and Fisher's exact tests and quantitative data were compared by analysis of variance, t-test. The continuous data was compared using nonparametric and parametric tests when indicated. Multivariate analysis was performed using one-way MANOVA. IBM® SPSS® Statistics version 25.0 was used to perform the analysis. The significance level was set at $p < .05$. Missing data was excluded from the statistical analysis.

Results

Demographic data and clinical characteristics of patients

In the present study, it was included 266 pregnancies of 173 patients followed in at our Centre between the years of 1993 and 2023. The average age at conception was 31.5 ± 5.1 years, the minimum age being 20 years old and the maximum 48 years old. The percentage of primiparity was 49.6%, the average age of diagnosis of SLE patients was 23.5 ± 6.4 years and the evolution of the disease was 7.9 ± 5.5 years. Table I summarizes the demographic and clinical characteristics of the patients before pregnancy.

Regarding SLE pre-conceptional manifestations, 82.9% of patients had mucocutaneous involvement, 67.3% articular manifestations, 44.5% hematologic involvement, 17.8% of patients had lupus nephritis and a lesser percentage of 6.1% and 3.8% had neurologic and cardiopulmonary manifestations, respectively. APS was present in 23.8% of patients, 47.6% fulfilling obstetric criteria (recurrent miscarriage in 25%) and 36.5% with thrombotic criteria. Other autoimmune diseases were present in 23.3%, with Hashimoto's thyroiditis being the most prevalent, 7.8%, followed by Sjogren syndrome, 5.6%. Arterial hypertension at conception was present in 13.9% of the patients.

The autoantibodies accessed at preconception were the ANA, present in 93.9% of pregnant women, anti-dsDNA detected in 40.5%, anti-SSA in 29.4%, anti-SSB in 5.3%, LAC was found in 16.7% of patients, aCL in 34.2% and anti-B2GPI in 19.8%.

Complement level at conception was low in 27.9% (low c3 in 27.1% and low c4 in 25.9%). The preconception disease activity was low (SLEDAI<=4) in 93.3% of women, moderate in 6%, high in 0.8%, and 83.1% were in remission on medication.

The pharmacologic treatment of SLE includes antimalarial agents such as hydroxychloroquine (HCQ), immunosuppressors (Azathioprine (AZA), Calcineurin inhibitors - Cyclosporine and Tacrolimus) and corticosteroid therapy. 80.1% of the patients were under treatment, 67.3% with HCQ, 40.6% with corticosteroid, 10.9% with azathioprine and 2.3% with calcineurin inhibitors. Additionally, 9.4% of pregnant women needed intravenous immunoglobulin. ASA was prescribed in 88.7% of women at the time of conception.

Pregnancy outcomes

Pregnancy outcomes are summarised in Table II. The live birth rate in our study was 86.7%, and the average gestational age at delivery was 37.2 ± 2.4 weeks. The average weight of the neonatal was 2850.0 ± 546.8 grams, with a minimum of 480 and a maximum of 4238 grams. The percentage of caesarean births was 47.1% and the rate of APO was 36.1% (risk factors for APO are summarized in Table III).

14.3% of the patients had a miscarriage, there were two cases of fetal death and six cases of termination of pregnancy before viability (two cases due to fetal malformation (0.7%), three cases due to fetal aneuploidy (1.1%) and one case at 20 weeks of pregnancy due to severe lupus flare refractory to medical treatment (0.3%)). The use of preconception ASA was significantly associated with the reduction of miscarriage as well as the use of AZA.

The rate of preterm delivery (PTD) in our study was 15.2%, spontaneous in 37,2% (Premature Rupture of Membrane in 17.1% of the patients) and 62,8% therapeutic (28.5% due to fetal indication and 37.1% to maternal indication). PTD was significantly associated with LAC and low c3 complement in the third trimester. A SLEPDAI<4 in every trimester demonstrated a significant association with the reduction of PTD. Additionally, PTD was more common in patients with HDP such as gestational hypertension, preeclampsia and HELLP.

The prevalence of Preeclampsia was 10.5%, HELLP was 1.6% and gestational hypertension was 8.9%. History of lupus nephritis, chronic arterial hypertension, SLE flare during pregnancy and the use of corticosteroids were associated with these pathologies. HCQ and remission of the disease, SLEPDAI<4 in all three trimesters demonstrated a preventive association with Preeclampsia and gestational hypertension. Periconceptional hypocomplementemia, especially low c4, and the use of anti-hypertension drugs, intravenous immunoglobulin and calcineurin inhibitors were significantly associated with Preeclampsia. Hypocomplementemia, c3 and c4, in the first trimester, was correlated with the development of HELLP.

FGR was present in 14.6% of the pregnancies. There was a significant association with many factors such as a history of hypertension, APS, lupus nephritis, anti-dsDNA antibodies, and LAC. Preconception depletion of c3 complement, as well as in the second and third trimesters and the use of an anti-hypertension medicine and AZA were negatively associated with FGR. It was

also more frequent in women with Preeclampsia and HELLP. Remission of SLE during all pregnancy demonstrated a reduction in the incidence of FGR.

GD affected 5.1% of pregnant women. In this study, it was not demonstrated a connection between the administration of corticosteroids, prednisolone, and the development of GD. ASA was proven to be a protective element against GD.

The caesarean rate was 47.1%, 30.8% was due to Obstetric contraindications for vaginal delivery like previous history of uterine surgery, malpresentation of the fetus and placenta previa; 20.2% was because of non-reassuring fetal state and 12.5% secondary to maternal deterioration. 60.1% of vaginal delivery occurred after induction and vaginal delivery after induction was 62.8%.

Neonatal outcomes

There were 229 newborns (one twin delivery), one of which died in the neonatal period due to severe prematurity (24 weeks of gestation). 11.2% of newborns were admitted to a neonatal intensive care unit (NICU) and 2.7% (6) had an Apgar at the 5-minute score of 7 or less, two of them with confirmed sepsis and one with asphyxiation. Interarticular communication was verified in eight newborns as well as three cases of pyelocaliceal dilatation. 15.1% (23) of newborns were below the 10 percentile of weight, with nine being admitted to a NICU. A history of arterial hypertension and LAC were associated with low birth weight. Lupus nephritis, and prednisolone usage, were significantly associated with admission to the NICU.

Lupus neonatal occurred in 5.8% of cases (13 newborns), two of which had complete heart block (0.9%) and anti-SSA and anti-SSB maternal autoantibodies, seven had fetal anti-SSA autoantibodies and eleven had a photosensitive rash that resolved during the first year of life. In our study, we found a significant association between the former maternal autoantibodies and neonatal lupus and CHB, and a correlation of concomitant autoimmune disease and CHB. HCQ did not demonstrate a significant association in the reduction of neonatal lupus.

Maternal outcomes

Regarding maternal outcomes, pre-conceptional remission was obtained in 92.9% of the patients and SLE improvement was seen in 9.4% of pregnant women.

SLE flares occurred in 15.3% of cases during pregnancy (26.3% in the first trimester, 18.4% in the second trimester and 36.8% in the third) and 14.2% during the first six months of postpartum. Of the flares observed approximately 31.6% had renal involvement, 15.8% mucocutaneous involvement, 13.2% had hepatic and the same percentage articular manifestations. Hypocomplementemia was verified in 50% of the patients and 10.5% had symptoms of central nervous system involvement. Nonetheless, no maternal death occurred in our study.

During pregnancy one patient had a stroke, at the 27th week of gestation. This patient had positive aCL and anti-B2GPI autoantibodies, however, it did not fulfil the criteria for APS.
Three women suffered from severe persistent headaches non-responsive to opioid treatment (lupus headache) during pregnancy and in one patient during postpartum, hypertension or eclampsia were not present. In these cases of neurologic involvement, there was one case of stillbirth at 26th week of pregnancy, one miscarriage in the first trimester and one PTD due to premature rupture of membranes at 31 weeks of gestation (patient with the stroke) and one vaginal delivery at 37th week of gestation after successful flare control. The SLE flares were treated with corticosteroids and in 10.5% with additional administration of AZA. In two patients, termination of pregnancy was decided due to the difficulties in controlling flares and maternal conditions, one case occurring before viability of the fetus, due to severe renal flare unresponsive to treatment.

SLE flare during pregnancy was significantly associated with pre-conceptional SLEDAI>4 and hypocomplementemia, a history of arterial hypertension, the use of corticosteroids, Prednisolone and the autoantibody anti-B2GPI. Remission of the disease in the second and third trimesters, the presence of anti-dsDNA antibodies in all duration of the pregnancy, the decrease in c3 and c4 in the first trimester, and c4 in the third trimester were associated with lupus flare during pregnancy and postpartum, as well as the decrease in the platelet number in the second trimester. Lupus nephritis, preeclampsia and HELLP were also associated with SLE flares during pregnancy and postpartum. However, gestational hypertension was only associated with flares during pregnancy. Postpartum flares were linked to a decrease in the number of platelets in the third trimester and with flares during pregnancy.

SLE improvement was significantly associated with remission of the SLE in the first trimester and the use of HCQ as chronic medication.

Discussion

Our study corroborates the idea that pregnancy in women with SLE is considered high-risk.[9,23] It results in a higher number of APO such as PTD, FGR, a higher rate of miscarriage and HDP as well as a higher rate of caesarean.[5,24,25]

Regardless of the control of the base disease, our analysis revealed that 92.9% of the patients had a SLEDAI score of under 4 (no/low activity), and the percentage of APO and pregnancy complications is far higher than in the general population.[24-30] In the preconception evaluation of the disease, it was noted that the most common findings in SLE patients were a positive serologic marker, with a depletion of complement and an increase in anti-dsDNA antibodies. However, neither demonstrated an association with the occurrence of APO.[31]

The percentage of live births in our study was 86.7%, comparable with the general population. The incidence of APO was 36.1%, the most common being PTD affecting 15.2% of the pregnancies, followed by FGR in 14.6% and miscarriage with a percentage of 14.3%, and, lastly, 10.5% of women developed preeclampsia. These findings are in accordance with the recently published data.[24,32-35] We found that there were some significant risk factors for the development of APO, an example being a history of arterial hypertension, a preconception SLEDAI score greater than 4, hypocomplementemia and the presence of LAC and SLE flares during pregnancy. A previous diagnosis of APS was significantly associated with FGR.[36]

HDP were assessed in our study. The incidence of preeclampsia was similar to the one reported in recent studies.[35,37] The development of preeclampsia was linked to a previous history of arterial hypertension, renal impairment, lupus nephritis, and Prednisolone-based treatment. These risk factors also had a significant association with the development of HELLP and gestational hypertension. The usage of HCQ demonstrated having a protective association with preeclampsia and gestational hypertension.[38] The points mentioned above can help explain the higher incidence of APO in this population.

The prescription of ASA in 88.7% of pregnant women since the beginning of gestation can justify the similar incidence of HDP and other pregnancy complications to the recent articles [39], which is much lower than what was reported in the older studies.[40-42]

It is relevant to note that the SLE flare and preeclampsia can present with the same symptoms, therefore it can be challenging to make a differential diagnosis, especially when the SLE flare is severe and when termination of pregnancy is considered.

The percentage of prematurity observed in our study was 15.2% which is lower than the current reported data.[33,35,43] SLEDAI score lower than 4 during all gestation demonstrated a protective connection with PTD, while the LAC detection and the presence of HDP were significantly associated with PTD. Hence, we can deduce that our low PTD rate is due to a stricter and more effective control of SLE.

The miscarriage percentage was 14.3%, which is similar to the stated in recent reports.[32-35] This percentage may be explained by a high detection rate. Due to the early evaluation of most patients, our Centre is able to detect pregnancies at earlier stages and consequently detect the occurrence of miscarriage that would not otherwise be accounted for. The use of ASA demonstrated a significant association with the prevention of miscarriage as well as the use of AZA.

The caesarean rate reported was 47.1%, similar to the published data.[33-35,42] This percentage can be explained by the higher number of complications, such as HDP, and other APO, in women with SLE.[23-25,44] Nonetheless, vaginal delivery is still advised and encouraged if there are no contraindications for such.

Concerning neonatal outcomes, there was a neonatal death due to severe prematurity, and the incidence of lupus in newborns was 5.8%, which resolved spontaneously in the first years of life. There were two cases of complete heart block observed corresponding to 0.9% of the newborns. The incidence of CHB in recent studies of patients with anti-SSA/B is 2%, however, it can rise to 20% if there is a previous history of this complication.[45-49] HCQ appears to be protective against this complication.[50] Despite our study not proving to have a significant association with CHB, it may justify our low incidence of this severe outcome.

SLE flare was witnessed in 15.3% of pregnancies and the absence of preconception remission, history of lupus nephritis, arterial hypertension and treatment with Prednisolone are significantly linked to the occurrence of flares.[33,51] The incidence of flares reported in other studies suggests that there is an increase in the number of flares during pregnancy.[9] The incidence observed in our study was lower than the recently published data.[33-35,42,52] The low rate of flares reported can be explained by the rigorous control and vigilance of the baseline

disease at preconception and also during gestation of our patients.[53,54] The use of HCQ in this study was not proven to be significantly associated with the reduction of SLE flares.

Lupus nephritis is a well-known risk factor for most SLE patient pregnancy complications such as flares, APO, HDP and PTD.[51,55,56] In our findings, renal impairment was frequent in SLE flares, 31.6% of cases. Additionally, proteinuria and hypocomplementemia were more frequent in women with a previous history of lupus nephritis. It is important to note that despite good control of the disease, patients with renal involvement are at an increased risk of SLE flare and APO.

The number of women with SLE who are able to get pregnant and have a successful pregnancy is increasing. When comparing our current data with studies made in our Centre,[57,58] we can witness a substantial reduction in the incidence of flares in pregnant patients (31% vs 16.3 % vs 15.3%), this can be justified by the increase in the treatment provided (39% vs 79.5% vs 80.1%).[57,58]

HCQ is a pregnancy-safe medication, not related to fetal malformation or APO, and it is considered to be a crucial element in disease control and management.[2,23,54,59]

Regarding the limitation found in this study, there is missing information and there may be some inaccuracy due to the retrospective nature of this work. Moreover, the number of patients and pregnancies encompassed is small which can be attributed to the low prevalence of SLE in the general population. Despite this, the sample size of our study enabled us to provide statistical significance for several variables. Another important aspect is the uniformity in prenatal follow-up offered by our institution's protocol of assistance, guaranteeing technical consistency and rigorous follow-up.

Conclusion

Our study corroborates the improvement of pregnancy outcomes reported in recently published data. Differing from the records published in the second half of the last century, the information obtained over the recent decades, including our study, proves that better control of the disease before and after gestation, and the administration of the appropriate treatment, particularly hydroxychloroquine, provides superior obstetric outcomes.

Nevertheless, pregnancy in women with SLE is still associated with high-risk scenarios, where SLE flares are frequent and correlated with the development of APO.

In our work, it was possible to conclude that miscarriage, PTD and HDP as well as FGR are statistically linked with active SLE.

In addition, using secure and effective immunosuppressive and immunomodulatory therapies has reduced disease activity during pregnancy and appears to be associated with a lower probability of the development of HDP. Despite the use of these therapies and apparent control of the disease, it is not possible to avoid some notable negative results, as APO still occurs in patients with well-controlled disease.

To conclude, it is conceivable to state that improving these outcomes is only feasible with the presence of trained multidisciplinary teams, with rigorous surveillance measures, beginning with a preconception evaluation, months prior to pregnancy itself, which constitutes the baseline for qualified antenatal care for SLE patients.

Tables

Table I. Baseline clinical characteristics of pregnant SLE patients.

	Mean	SD	Count	N %
Age of conception	31.5	5.1		
Obstetric history				
Nulliparity			132	49.6%
Previous miscarriage			69	25.9%
Assisted reproductive technology			12	4.5%
Previous comorbidities				
Concomitant Autoimmune disorders			62	23.3%
APS			63	23.8%
Arterial hypertension			37	13.9%
Periconceptional SLE status				
SLEDAI≤4 at conception			237	93.3%
Remission on medication			212	83.1%
Previous lupus nephritis			47	17.8%
Previous mucocutaneous manifestations			218	82.9%
Previous articular manifestations			177	67.3%
Previous cardiopulmonary manifestations			10	3.8%
Previous hematologic manifestations			117	44.5%
Previous neurologic manifestations			16	6.1%
Autoantibodies				
ANA			247	93.9%
Anti-DsDNA			107	40.5%
Anti-Ro (SSA)			77	29.4%
Anti-LA(SSB)			14	5.3%
Lupus Anticoagulant			43	16.7%
Anti-cardiolipin			90	34.2%
Anti B2GP1			52	19.8%
Medication				
HCQ			179	67.3%
Prednisolone			108	40.6%
Immunoglobulin			25	9.4%
Azathioprine			29	10.9%
Calcineurin inhibitors			6	2.3%
Antihypertensive			24	9.1%
Vitamin D			44	17.1%
ASA			236	88.7%
LMWH			99	37.2%

ANA: antinuclear antibodies; APS: antiphospholipid syndrome; ASA: low-dose acetylsalicylic acid; HCQ: hydroxychloroquine; LMWH: low-molecular- weight heparin; SLE: systemic lupus erythematosus; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index.

Table II. Pregnancy outcomes of pregnant women with SLE.

	Column N %	Mean	SD
Pregnancy outcome			
Live birth	86.7%		
Mean gestational age at delivery		37	2
APO	36.1%		
Miscarriage	14.3%		
PTD	15.2%		
Gestational diabetes	5.1%		
HELLP syndrome	1.6%		
FGR	14.6%		
Caesarean delivery	47.1%		
Neonatal outcomes			
Neonatal deaths	0.4%		
Stillbirths	0.8%		
Neonatal ICU admission	11.2%		
Neonatal lupus	5.8%		
Maternal outcomes			
SLE improvement	9.4%		
Maternal deaths	0%		
SLE flare during pregnancy	15.3%		
SLE flare postpartum	14.2%		

APO: adverse pregnancy outcome; FGR: fetal growth restriction; HELLP: hemolysis, elevated liver enzymes, and a low platelet count syndrome; ICU: intensive care unit; PTD: preterm delivery; SLE: systemic lupus erythematosus.

Table III. Risk factors for APO

Variable	Normal Pregnancy (n=171)	APO (n = 95)	p-value
Previous comorbidities			
Arterial hypertension	10 (5.8%)	27 (28.4%)	<0.05
APS	34 (20.4%)	28 (29.5%)	NS
Previous lupus nephritis	20 (11.7%)	27 (28.4%)	<0.05
SLE status			
SLEDAI≤4 at conception	156 (96.3%)	80 (88.9%)	<0.05
SLE flare during pregnancy	16 (9.4%)	21 (22.1%)	<0.05
SLE improvement	17 (10.2%)	7 (8.0%)	NS
SLE flare postpartum	22 (13.2%)	12 (21.0%)	NS
Low complement at conception	38 (24.1%)	34 (35.7%)	NS
Low complement during gestation	25 (14.6%)	32 (36.8%)	<0.05
Medication			
HCQ	113 (67.3%)	64 (67.4%)	NS
Prednisolone	65 (38.7%)	49 (51.7%)	NS
Azathioprine	20 (11.9%)	9 (9.5%)	NS
Calcineurin inhibitors	4 (2.4%)	2 (2.1%)	NS
Vitamin D	29 (17.7%)	15 (16.3%)	NS
ASA	154 (91.7%)	80 (84.2%)	NS
LMWH	61 (36.3%)	37 (38.9%)	NS
Autoantibodies			
Anti-DsDNA	64 (38.3%)	47 (49.5%)	NS
Anti-Ro(SSA)	38 (22.2%)	37 (38.9%)	NS
Anti-LA(SSB)	11 (6.7%)	4 (4.2%)	NS
Lupus Anticoagulant	18 (11.1%)	23 (25.0%)	<0.05
Anti-cardiolipin	57 (34.3%)	34 (35.8%)	NS
Anti B2GP1	30 (18.1%)	21 (22.3%)	NS

ANA: antinuclear antibodies; APS: antiphospholipid syndrome; ASA: low-dose acetylsalicylic acid; HCQ: hydroxychloroquine; LMWH: low-molecular-weight heparin; SLE: systemic lupus erythematosus; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index.

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