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Hydroxychloroquine and Pregnancy on Autoimmune Diseases

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RESUMO

Introdução: Os fármacos antimaláricos, como a Hidroxicloroquina, têm sido cada vez mais utilizados no tratamento de doenças autoimunes, como o Lupus Eritematoso Sistémico, o Síndrome Antifosfolipídico e o Síndrome de Sjögren. Pensa-se que este fármaco, atue de vários modos, com propriedades antioxidantes, anti-inflamatórias, imunomodeladoras e anti-trombóticas. De acordo com o *American College of Rheumatology*, o uso de hidroxicloroquina encontra-se aconselhando para todas as mulheres com Lupus Eritematoso Sistémico, sempre que possível. Em doentes com Síndrome Antifosfolipídico, o uso de hidroxicloroquina, em associação com anticoagulantes orais reduz a ocorrência de eventos trombóticos. Ainda que, não exista um tratamento específico aprovado para o Síndrome de Sjögren, a utilização de hidroxicloroquina para a dor musculoesquelética, tem sido a 1ª linha no tratamento.

Objetivo: O objetivo do presente artigo, é investigar o efeito da hidroxicloroquina em mulheres grávidas com doenças autoimunes como o Lupus Eritematoso Sistémico, Síndrome Anti Fosfolipídico e Síndrome de Sjögren, bem como comparar a prevalência de complicações materno-fetais, neonatais e a evolução da doença de base.

Métodos: Análise retrospetiva de gestações de mulheres com Lúpus Eritematoso Sistémico, Síndrome Anti fosfolipídico e Síndrome de Sjögren que foram medicadas com hidroxicloroquina entre 2015 e 2020 no serviço de Obstetrícia da Unidade de Medicina Materno-Infantil do Centro Materno Infantil do Norte em comparação com dois grupos- um que consiste em mulheres com as patologias suprarreferidas e que não foram medicadas com hidroxicloroquina e outro que incluiu mulheres saudáveis vigiadas na mesma instituição, seguidas entre 2015 e 2020. Cada gravidez foi considerada como um evento. As manifestações da doença durante a gravidez, bem como o seu momento de aparecimento e o tratamento que realizaram, foram registadas.

Resultados: Entre 2015 e 2020, foram analisadas 94 gestações de mulheres com doenças autoimunes. Entre estas, 54 encontravam-se medicadas com hidroxicloroquina. Foi demonstrada uma relação estatisticamente significativa entre o uso de hidroxicloroquina durante a gravidez e a presença de fatores de risco para piores desfechos obstétricos. No entanto os desfechos maternos e neonatais adversos, não foram significativamente piores.

Conclusões: Ainda que os achados não sugiram que a hidroxicloroquina tenha melhorado os desfechos neonatais e maternos, devemos interpretá-los atentamente, uma vez que no grupo de estudo, as doentes apresentavam mais fatores de risco para desfechos obstétricos adversos.

Assim, atendendo a que não se verificaram piores desfechos obstétricos no grupo de estudo, conclui-se o efeito protetor da hidroxicloroquina.

Key Words: Pregnancy, Sjogren's Syndrome, Antiphospholipid Syndrome, preeclampsia, antimalarial drugs, Systemic Lupus Erythematosus, Hydroxychloroquine, Lupus pregnancy, antimalarials, recurrent miscarriage

ABSTRACT

Introduction: Antimalarial drugs, such as hydroxychloroquine, are widely used to treat rheumatoid diseases, such as Systemic Lupus Erythematosus, Antiphospholipid Syndrome and Sjogren's Syndrome. Hydroxychloroquine appears to have a range of effects depending on the target cells and disease pathophysiology, including antioxidant, anti-inflammatory, immunomodulatory, and antithrombotic pathways. Hydroxychloroquine is advised for all pregnant women with Systemic Lupus Erythematosus if possible, according to the American College of Rheumatology. Combining hydroxychloroquine with oral anticoagulants has been shown to minimize thrombotic recurrences in Antiphospholipid Syndrome as well. Sjogren's Syndrome presently has no approved therapy or remission agent. However, the treatment of inflammatory musculoskeletal pain with disease-modifying antirheumatic drugs follows a stepwise pattern, with hydroxychloroquine being the first-line therapy.

Aim: This study aims to see how hydroxychloroquine affects pregnant women with autoimmune illnesses such as Systemic Lupus Erythematosus, Sjogren Syndrome, and Antiphospholipid Syndrome. It also aims to investigate the prevalence of fetal, maternal, and neonatal complications.

Methods: Retrospective analysis of all pregnancies of women with Systemic Lupus Erythematosus, Sjogren's Syndrome, and Antiphospholipid Syndrome who were taking hydroxychloroquine between 2015 and 2020, in Obstetrics and Gynaecology Department, Centro Materno Infantil do Norte, Centro Hospitalar Universitário do Porto. Comparison between two groups, one which consisted of women with autoimmune diseases who were not treated with hydroxychloroquine and another that included healthy pregnant women, who were followed in our institution, between the same period. Each pregnancy was considered an event. The manifestations of diseases, as well as when they appeared and the treatment they received during pregnancy, were registered.

Results: Between 2015 and 2020, 94 pregnancies of women with autoimmune diseases were analysed. 54, were taking hydroxychloroquine during pregnancy. There was a significant correlation between the use of hydroxychloroquine during pregnancy and factors who predict worst pregnancies outcomes. However, no significant differences were detected for maternal and neonatal outcomes.

Conclusions: Even though our findings did not suggest that hydroxychloroquine improved newborn or maternal outcomes, this should be regarded carefully because in our study group,

autoimmune patients who used hydroxychloroquine had greater risk factors for unfavourable obstetric outcome. Because no major differences were seen in this group, the usage of hydroxychloroquine was concluded to be protective.

Key Words: Pregnancy, Sjögren's Syndrome, Antiphospholipid Syndrome, preeclampsia, antimalarial drugs, Systemic Lupus Erythematosus, Hydroxychloroquine, Lupus pregnancy, antimalarials, recurrent miscarriages.

LIST OF ABBREVIATIONS

ACOG- American College of Obstetricians and Gynaecologists Committee

ACR- American College of Rheumatism

ANA- Antinuclear antibodies

APO- Adverse pregnancy outcomes

APS- Antiphospholipid Syndrome

ASA- Low dose acetylsalicylic acid

CHB- Congenital heart block

EULAR- European League Against Rheumatism

FGR- Fetal growth restriction

GD- Gestational diabetes

HCQ- Hydroxychloroquine

HDP- Hypertensive disorders of pregnancy

IADPSG- International Association of Diabetes and Pregnancy Study Groups

ICU- Intensive Care Unit

LAC- Lupus Anticoagulant

LMWH- Low molecular weight heparin

PE- Preeclampsia

pSS- Primary Sjogren Syndrome

PTD- Preterm Birth Delivery

SLE- Systemic Lupus Erythematosus

SS- Sjogren's Syndrome

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INTRODUCTION

Chloroquine and hydroxychloroquine (HCQ) are 4-aminoquinoline weakly basic chemical. The synthetic variant of chloroquine-HCQ, differs from chloroquine because it has a hydroxyl group connected to a side chain, which is associated with the same effectiveness but a less toxic side-effect profile.[1] HCQ appears to have a variety of activities, including antioxidant, anti-inflammatory, immunomodulatory, and antithrombotic pathways, depending on the target cells involved and the disease pathophysiology. HCQ inhibits lysosomal activity, interferes with antigen processing in macrophages and other antigen-presenting cells, and inhibits Toll-like receptor-associated processes, reducing the generation of proinflammatory cytokines and other molecular pathways.[2,3] Antimalarial medications, like HCQ, are now commonly used to treat rheumatological illnesses such as Systemic Lupus Erythematosus (SLE), Antiphospholipid Syndrome (APS), and Sjogren's Syndrome (SS).[3] In addition, these drugs also have anti-platelet and hypolipemic properties.[4] The antiviral function of HCQ in the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) sickness has recently been questioned (COVID-19).[5]

HCQ appears to be safe to use during pregnancy and lactation.[5,4] However, because HCQ penetrates the placenta and suppresses cell division and DNA synthesis, it may have an effect on rapidly dividing embryonic cells.[6] But, when compared to other rheumatology medicines (such as methotrexate, mycophenolate, and cyclophosphamide), HCQ has a much safer profile. [5]

SLE is a multi-organ chronic autoimmune disease that primarily affects women between late adolescence and early forties. The disease activity of SLE fluctuates, with periods of high disease activity (flares) followed by periods of low activity. [2,7,8,9] Due to the concomitance of the disease with childbearing age, this condition can be quite common during pregnancy. For these individuals, reproductive issues as well as illness care throughout pregnancy are critical considerations.[8] Women with SLE are more likely to have disease flares during pregnancy, especially if they have had previous high disease activity noticed within four months of conception, history of lupus nephritis, and discontinuation of HCQ treatment.[7] When compared to the general population, women with SLE have a higher risk of fetal and maternal adverse pregnancy outcomes (APO), including prematurity, fetal growth restriction (FGR), preeclampsia (PE), and fetal loss, all of which increase maternal morbidity and mortality, as well as neonatal lupus due to autoantibody transplacental passage.[10] SLE patients also face a variety of medical issues, including thrombosis, nephritis, and infectious diseases.[2]

SLE care nowadays focuses on preconception counselling to determine disease activity, drug regimen, and effective contraception alternatives until illness remission is achieved.[11] Women are now advised to avoid pregnancy during active disease and to wait at least 6 months following disease remission.[12]

According to the 2020 American College of Rheumatology (ACR), HCQ is recommended for all pregnant women with SLE if possible, and it has not been linked to an increase in congenital abnormalities, spontaneous abortion, or fetal death when used during pregnancy.[13–15,27] As a result, using HCQ during pregnancy is part of a better disease management strategy, as it is expected to enhance pregnancy outcomes due to its anti-inflammatory and immunomodulatory properties.[8,13] A decrease in cholesterol and glucose levels, as well as an anti-thrombotic action, are among the positive therapeutic benefits. More significantly, due to the decrease in illness flares associated with its administration, it plays a critical role in the treatment of SLE. HCQ also has other advantages, such as extending pregnancy and lowering the rate of FGR without causing teratogenic consequences or long-term morbidity in the newborn.[16]

Moreover, several studies have found that HCQ can help prevent PE and that SLE and PE have similar underlying pathophysiology. Chronic inflammation and oxidative stress raise the risk of hypertension, stroke, and kidney illness in SLE patients. In PE, oxidative stress causes syncytiotrophoblast apoptosis and excessive placental release of antiangiogenic factors like activin A, soluble fms.like tyrosine kinase receptor-1, soluble endoglin, and proinflammatory cytokines such as tumour necrosis factor-alpha (TNF-alfa) into the maternal circulation, leading to endothelial dysfunction and stimulation of endothelin-1 production.[2]

APS is an autoimmune condition characterized by a correlation between thrombotic events and/or obstetric morbidity in people who have antiphospholipid antibodies (aPL). Recurrent early pregnancy loss (less than 10 weeks gestation), late fetal loss (more than 10 weeks gestation), delivery at less than 34 weeks gestation due to ischemic placental insufficiency, and other manifestations of placental insufficiency such as FGR, PE, eclampsia, placental abruption, and HELLP syndrome are all manifestations of this disease. Antibodies to cardiolipin, β2-glycoprotein, and lupus anticoagulant (LAC) are included in the categorization of APS.[17] APS can appear isolated (primary APS) or with other autoimmune disease (associated APS). Patients with obstetrical APS are advised to take low-dose aspirin (ASA) or a combination of low-dose aspirin and low molecular weight heparin (LMWH). [18] The addition of HCQ to oral anticoagulants, on the other hand, has been shown to prevent thrombotic recurrences.[19,20] Rand et al, demonstrated that HCQ may prevent the binding of APL - 2-glycoprotein I complexes to phospholipid bilayers using ellipsometry and atomic force microscopy. On the other

hand, Annexin A5 is a phospholipid bilayer crystallizing protein. APL impair annexin A5 binding, preventing this powerful anticoagulant protein from working. APL can be reversed by HCQ, restoring annexin A5 binding to phospholipid bilayers and thereby preserving annexin A5 anticoagulant action against disruption by antiphospholipid antibodies. [20]

SS is a chronic autoimmune disease, that can present alone as primary Sjogren Syndrome (pSS), or in the context of another autoimmune disease, such as SLE, as secondary SS.[21] This condition primarily affects women, with a female to male ratio of at least 9:1 and a mean age at diagnosis of approximately 50 years.[22] For pSS, evidence on pregnancy outcomes is currently scarce. Congenital heart block (CHB), which is a symptom of neonatal lupus, is the most well-known and dangerous consequence. Neonatal lupus is an autoimmune illness caused by the transplacental transmission of anti-RO(SSA) and/or anti-LA antibodies (SSB).[23] Anti-Ro/SSA and anti-La/SSB antibodies are most commonly linked with pSS, although they can also be seen in SLE patients and healthy people.[21] Neonatal lupus affects 1-2 percent of babies born to women who have autoimmune illnesses, most commonly in SLE and SS.[23] SS is one of the most challenging chronic autoimmune rheumatic conditions to diagnose and treat. There is currently no on-label treatment or remission agent for SS.[24] SS may cause inflammatory arthralgias, myalgias, and synovitis, which all contribute to disease morbidity and disability. The use of disease-modifying antirheumatic drugs (DMARDS) for the treatment of inflammatory musculoskeletal pain follows a progressive strategy, with HCQ being the first-line therapy.[22] Neonatal lupus and SS-A-related fetal block are also less likely.[5]

In this investigation paper, the aim is to evaluate how HCQ affects pregnant women with autoimmune illnesses and the prevalence of fetal, maternal, and neonatal complications, with and without its use.

MATERIAL AND METHODS

Selection of Patients

This retrospective study included pregnant women with SLE, APS and SS who were managed at the Obstetrics Department and at the Immunology Clinical Unit of a tertiary university hospital (Centro Hospitalar Universitário do Porto), between January 2015 and December 2020. For SLE diagnosis, all patients accomplished the ACR and European League Against Rheumatism (EULAR) criteria; the EULAR and Sidney criteria for APS diagnosis; and the ACR criteria for SS diagnosis.[19-24] This research evaluated 94 pregnancies, in women with autoimmune diseases and 215 pregnancies of healthy women. Because preconception clinical state was used as a predictive result, each pregnancy was looked at separately. The study group consisted of women with SLE, APS, and SS who took HCQ during pregnancy. There were two control groups, which consisted of women with autoimmune diseases who did not take HCQ, and another group, which contained healthy women who visited the same hospital at the same time. Twin pregnancies were excluded because of its association with other concomitant risks that could bias results.

In all groups, baseline maternal data was obtained, including age, previous obstetric history, and previous medical problems. Early embryonic loss, mother's complications (thrombosis, PE, HELLP syndrome, diabetes, gestational hypertension), fetal complications (intrauterine deaths, FGR, uterine Doppler abnormalities), date of beginning and characteristics of treatments, delivery, birth weight, Apgar, and neonatal complications were all evaluated in the study group and in the non-HCQ group. All lupus flares and other lupus related comorbidities were assessed. The pharmacotherapy used in women before and during pregnancy was also gathered.

Antinuclear (ANA), anti-double stranded DNA (anti-dsDNA), anti-Ro/SS-A and anti-Ro/SS-B, anti-cardiolipin, and anti-2 glycoprotein antibodies, LAC, and C3 and C4 complement components were also evaluated in the baseline laboratory data.

Medicine and Obstetrics Management Protocol

Regular obstetric and internal medicine appointments were scheduled throughout pregnancy with the aim to early detect SLE flares, hypertensive disorders of pregnancy (HDP (gestational hypertension/PE/hemolysis, increased liver enzymes, and a low platelet count syndrome (HELLP)), gestational diabetes (GD), FGR, CHB, and risk assessment for preterm birth

delivery (PTD). As a result, preconception counselling is required, and pregnancy should only be planned six months upon remission of disease.

Pregnant women with autoimmune illnesses should have their haematological, chemical, and immunological parameters monitored on a regular basis, as the research group did and the non-HCQ group did. Women were also subjected to prenatal sonography with doppler and fetal echocardiogram on a regular basis.

The low-risk pregnancies in the healthy women's group were handled according to Portuguese guidelines. Serial laboratorial monitoring was undertaken on these individuals, as well as one ultrasound scan every trimester for fetal assessment.[25]

Fetal and Obstetric Outcomes

Maternal and fetal outcomes were assessed. Birth weight, gestational age at delivery, Apgar scores at 1 and 5 minutes after birth, neonatal intensive care unit hospitalization, development of neonatal lupus or CHB, existence of congenital malformation or respiratory distress syndrome were among the fetal outcomes studied.

Miscarriage, stillbirth, FGR, PTD, or the development of HDP were all considered APO.

The unexpected loss of a fetus before 20 weeks of gestation was characterized as spontaneous abortion, stillbirth was defined as the fetus's death after 20 weeks of gestation, and elective abortion was described as the purposeful termination of pregnancy.

PTD referred to a live birth before the 37th week of gestation. Using the Portuguese population's curves, FGR was defined as a birth weight below the 10th percentile.[26] Low birth Weight was defined as birth weight below 3rd percentile.

PE was defined as a systolic blood pressure ≥ 140 mmHg and/or a diastolic blood pressure ≥ 90 mmHg on two occasions at least 4 hours apart after 20 weeks of pregnancy in a woman with previously normal blood pressure and proteinuria (defined as urinary excretion of 300 mg or more in 24 hour urine collection or protein/creatinine ratio of 0,3 mg/dL or dipstick reading of 2+) according to American College of Obstetricians and Gynaecologists Committee (ACOG) criteria (2020). Alternatively in the absence of proteinuria, PE is defined as a new-onset hypertension with the new onset of target organ damage (platelet count less than 100,000x109/L, serum creatinine concentration greater thar 1,1 mg/dL or doubling of the serum creatinine concentration in the absence of other renal diseases, elevated blood concentrations of liver transaminases to twice the upper limit of normal concentration, severe persistent right

upper quadrant or epigastric pain and not accounted for by alternative diagnoses, and pulmonary edema or new-onset headache unresponsive to acetaminophen and not accounted for by alternative diagnoses or visual disturbances). ACOG criteria (2020) defines Gestational Hypertension as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥90 mmHg, on two occasions at least 4h apart after 20 weeks of gestation, in a woman with previously normal blood pressure in the absence of proteinuria and that returns to normal in the postpartum period.[27]

GD was defined according to the Portuguese Endocrinology Society guidelines for the diagnosis of gestation diabetes adapted from the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria.[28,29]

Statistical Analysis

Data was analysed using descriptive statistics. The Chi-Squared and Fisher's Exact tests were used to compare categorical data between groups, while the analysis of variance (ANOVA) and Scheffe's test were used to analyse quantitative data. Nonparametric (Mann-Whitney U test and Friedman test) and parametric (t tests and repeated measures ANOVA) tests were used to compare continuous data. The analysis was carried out using IBM SPSS Statistics version 26.0. The significance threshold was chosen at $p<0.05$.

The Medical Ethical Committee of Centro Hospitalar Universitário do Porto authorized the retrospective, observational design of this investigation. All patient information was kept private.

RESULTS

Demographic and Clinical Characteristics of Patients

Table I summarizes the principal pregestational demographic and clinical characteristics of all three groups.

The study group included 54 pregnancies, of which 42 had SLE, 8 SS, and 4 APS. The average age at conception in the study group was 33,11±5,244 years. The mean disease evolution time before pregnancy was 9,10±4,892 years and the mean age at disease diagnose was 24,23±6,516 years.

There were 40 pregnancies of women with autoimmune diseases who were not taking HCQ, with 10 having SLE, 6 SS, and 24 APS. The mean age at conception was 33,2±5,060 years. The average period for illness progression prior to conception was 4,42±5,411 years, while the average age at disease diagnosis was 28,67±6,787 years.

The healthy group included 215 pregnancies with an average age at conception of 30,75±5,733 years ($p<0,01$).

Primiparity was found to be 38.9% (n=21) in the study group, 27,5% (n=11) in the non-HCQ group, and 44.7% (n=96) in the healthy group. In the study group, 38.9% (n=21) had suffered prior miscarriages, compared to 47.5% (n=19) and 23.3% (n=50) in the non-HCQ group and the healthy group, respectively. FGR was shown to be more common in prior pregnancies among women who did not take HCQ than in women who did. However, no substantial link was discovered. In the research group, one episode of PE from prior pregnancies was documented.

Both groups of women with autoimmune disorders had similar rates of women reporting symptoms of their condition at the time of conception. In both groups, there was one occurrence of lupus flare 6 months before pregnancy. Only women in the study group were diagnosed with lupus nephritis. (p=0,569). Although no significant relationship was shown, the research group had a lower incidence of chronic arterial hypertension than the group of women who did not take HCQ.

Autoantibodies state was analysed in both groups. In the group of women who took HCQ, ANA were positive in 83,3% (n=45) of the cases, Anti-DsDNA in 37% (n=20), Anti-SSA in 27,8% (n=15), Anti-SSB in 9,3% (n=5), Anti-β2 Glycoprotein in 16,7% (n=9), Anti-Cardiolipin in 13% (n=7) and LAC was positive in 3 women. Complement was low in 18,5% (n=10) of patients.

There was a significant correlation between HCQ prescription and women with positive ANA (p<0,01), anti-DsDNA (p<0,01), positive anti-cardiolipin (p<0,01), positive Anti-β2 Glycoprotein (p<0,01) and positive LAC (p<0,01). There were more women with complement decrease in the research group, than in the non-HCQ group. (p<0,05).

In both groups, HCQ, immunosuppressors, and vitamins were used. Before pregnancy, 85,2% (n=46) of women were taking HCQ, 35,2% (n=19) were using ASA, 13,0% (n=7) were on LMWH, and 17% (n=31,5%) were taking prednisolone. During pregnancy, 92,6% (n=50) were on ASA, 53,7% (n=29) were on LMWH and 37% (n=20) were on prednisolone. There were more women prescribed with HCQ taking prednisolone than women who did not take HCQ during pregnancy, resulting in a significant relationship between the use of HCQ and prednisolone (p<0,01). On the other hand, despite the lack of a significant link, the percentage of women in the study group who were on LMWH during pregnancy (53,7%) was greater than in the non-HCQ group.

Pregnancy outcome

Pregnancy outcomes were expressed in Table II.

The study group and healthy group both had 100% (n=54) live birth rates, whereas the non-HCQ group had 92.1% (n=37). In this trial, all three newborn deaths occurred in individuals who were not taking HCQ. (p=0,089) The average gestational age at delivery in the study group was 37,5±2,4 weeks, compared to 36,87±3,256 weeks in the non-HCQ group. (p=0,6)

Although there was no significant difference between the HCQ and non-HCQ groups, the frequency of pre-term birth was lower in the HCQ group. (p=0,149)

The mode of delivery was assessed in all groups. In the HCQ group, 25,9% (n=14) of births were eutocic deliveries, 37% (n=20) were c-sections, 3 cases were distocic deliveries with forceps, and 14,8% (n=8) were distocic deliveries with suction cup.

The study group had a 50% (n=27) incidence of APO, compared to 60% (n=24) in the non-HCQ group. However, no substantial link could be found. (p=0,336) In the healthy group, the incidence was 17,2% (n=32). (p<0,01)

PTD was recorded in five pregnancies in the study group, and while there was no significant link between HCQ and PTD, only one case was reported in the non-HCQ group (p=0,232). In the healthy group, no instances were reported.

In the research group, one occurrence of GD was documented. Women who were not on HCQ had a greater prevalence of GD (p=0,080). A total of 9,3% (n=20) of cases were recorded in the healthy group. (p=0,093)

In the research group, two women developed Gestational Hypertension. Although there was a greater prevalence of Gestational Hypertension in women who were not using HCQ, there was no statistically significant link (p=0,395).

1 case of PE was diagnosed in the study group and 3 were reported in women who were not taking HCQ (p= 0, 309). There were no cases of eclampsia reported.

Women who were using HCQ and women who were not taking HCQ had similar rates of FGR. (p=1,000) In the healthy group, the incidence of FGR was 3,3 % (n=7) (p=0,33).

Pregnancy aggravated the symptoms of 15,1 % (n=8) of women prescribed with HCQ. Even though fewer women who did not take HCQ stated the same, there was no statistically significant link between these outcomes. (p= 0,262)

Neonatal Outcome

Neonatal outcomes were expressed in Table III.

The average newborn weight was 2902,73± 426,74g in the study group, 2763,03±751,365g in women who were not under HCQ (p=0,296) and 3148,90±489,53g in the healthy group (<0,01). There was a lower incidence of low birth weight (<P3), in newborns in the study group, when compared to the group of women who were not under HCQ (p=0,238).

The mean Apgar score at minute 1 in the study group was 8,50±1,191, whereas in the non-HCQ group was 8,24±2,376 (p=0,519) and 8,64±1,099 (p=0,448) in the healthy group. At the 5th minute, the research group's mean Apgar Score was 9,59±0,693, 9,21±2,315 in patients who did not take HCQ (p=0,302), and 9,71±0,664 in healthy women (p=0,282). Despite the lack of a meaningful link, the incidence of low Apgar scores during the first minute was lower in women prescribed with HCQ compared to those who were not on the medication (p=1,000) and healthy women (p=0,523). In the study group, there were no incidences of low Apgar scores at the 5^{th} minute. However, 4 infants in the non-HCQ group had a low Apgar score at minute 5, indicating that there is a significant link with HCQ use (p<0,05).

Neonatal complications were reported in fewer women from the study group (20,4%), then in women who were not taking HCQ (35%). However, there was no significant association

(p=0,19). Meanwhile, the healthy group (15.8%) had a lower incidence than the other two groups (p<0,01).

Women taking HCQ and those who were not taking HCQ had similar rates of infant Intensive Care Unit (ICU) admission (p=0,875). When compared to women on HCQ, the incidence in healthy women was considerably lower (p<0,01).

In the study group, 2 cases of CHB and 5 cases of newborns with positive anti-SSA/anti-SSB antibodies were recorded, while no reports were made in the group of women who were not taking HCQ. All instances of CHB required neonatal intervention and the implantation of a pacemaker. In none of the groups, significant abnormalities were reported.

Maternal Outcome

Table IV displays the Maternal Outcome.

Under HCQ, the prevalence of women experiencing symptoms during conception was identical to that of women who were not on HCQ (p=0,712).

There was one occurrence of SLE flare during pregnancy in a woman on HCQ (p=1). The described case showed ANA-positive autoantibodies, anti-DsDNA, and anti-SSA antibodies, as well as chronic arterial hypertension.

The incidence of SLE flare postpartum in women who were taking HCQ was higher compared to women who were not taking HCQ (p=1). All patients with SLE flare postpartum had positive ANA autoantibodies.

No maternal deaths were reported.

DISCUSSION

The impact of HCQ on unfavorable obstetric outcomes has been widely investigated. As a consequence of these articles confirming its efficacy and relative safety, HCQ has become more widely used in pregnant women with SLE, SS and APS in recent years. [2,7,8,13,15,15,16,18,30–34]. In this study, we investigated the association between HCQ use and disease activity as well as pregnancy and neonatal outcomes in a population of women with SLE, APS and SS.

Although, HCQ has been recommended for pregnant women with autoimmune diseases, especially SLE, in this 5-year analysis study, as shown in Table V, only 57,4% of women with autoimmune diseases were treated with his drug. [13–15,35]

HCQ was well tolerated, and no serious side effects were observed. Though long-term high-dose use has been linked to retinopathy, this can be prevented by using the lowest effective dosage.[34,36,37] There was no evidence of a higher chance of significant structural birth abnormalities, which was consistent with other studies.[31,38,39]

Most women (65,4%), who were under HCQ, decided to breastfeed. It should be noted that HCQ is compatible with breastfeeding, and women with SLE are advised to take HCQ not only during pregnancy, but also throughout breastfeeding to avoid postpartum flares.[7]

There was a significant correlation between the use of HCQ during pregnancy and the positive autoantibodies state for ANA, Anti-DsDNA, Anti-β2 glycoprotein and complement decreased. C3 and C4 levels are commonly used to monitor disease activity in patients with SLE. [41] Because the complement system is activated in SLE patients as the disease progresses and complement protein is produced, the degree of disease activity is assumed to be related to production, activation, and consumption, concluding that lower complement levels are associated with worse outcomes. [42] Hypocomplementemia has shown to be a predictor of lupus flares during pregnancy and worst pregnancy outcomes. [7,43] Autoantibodies against several intracellular components are produced in SLE and other autoimmune rheumatic disorders, such as Rheumatoid Arthritis, SS, Scleroderma, Raynaud's disease, Polymyositis, and Mixed Connective Tissue disease.[44] Antiantibodies that recognize and bind to DNA (anti-DNA antibodies) are essential biomarkers to investigate the mechanisms of autoimmunity SLE, and an increase in DNA binding is also associated with higher disease activity. [45] As shown, dsDNA autoantibodies were more prevalent in HCQ-exposed pregnancies, indicating that the HCQ-exposed group may has a higher illness severity and consequently a higher prevalence of worst pregnancy outcomes (FGR, for example). [15] ANA in the blood/serum are a defining feature of

SLE. They are useful not just for diagnosing the condition but also for tracking its course.[44] Anti-β2 glycoprotein is an aPL, that is, in association with anti-cardiolipin and LAC, considered as laboratory criteria for APS, according to Sidney Criteria.[46] It has been shown that aPL can cause thrombosis and fetal loss in people who have SLE, being related to worse disease and pregnancy outcomes.[47] Although there wasn't a significant relationship between Anti-RO/SSA, Anti-La/SSB, there was a higher percentage of these in women who were under HCQ. Following these findings, we could raise the possibility that the women from the study group, also had more predictive factors of worse outcomes.

There was also a significant correlation between the use of HCQ during pregnancy, and the prescription of prednisone. High-dose corticosteroids are used to assist limit disease development as the disease develops and clinical symptoms deteriorate.[47]

Even though there was not a statistic significant correlation, we can observe that there was a larger number of women prescribed with ASA, LMWH and cyclosporine, who were also under HCQ, suggesting that women who were prescribed with HCQ, tend to take more drugs to control disease activity.

These findings, suggest the possibility that woman in our study group, who were under HCQ, also had more predictive factors of worst outcomes. It should be noted that positive aPL, low complement levels and anti-SSA/SSB antibodies are linked to poor pregnancy outcomes.[34] Considering that the population in our study group, who were under HCQ, had more positive autoantibodies, complement decreased, and needed more pharmacotherapy to manage their disease, we could expect this women to have worst pregnancy outcomes. This suggests that women with moderate lupus and lower risk of worst pregnancy outcomes, may have been less likely to be administered HCQ, enhancing the non-HCQ group's pregnancy outcomes.

Sciascia et al. suggested that the use of HCQ during pregnancy, might result in a higher rate of live births in women with persistent aPL. [48] Ruffatti et al reported that starting HCQ- 400 mg/daily preconceptionally was more effective than other oral therapies in improving live delivery outcomes in refractory obstetric APS. HCQ was utilized alone or in combination with steroids or immunoglobulins in the previous research. Some of the patients had thrombotic APS or SLE, while others were from a high-risk APS group who had previously failed traditional therapy. [48,49] In addition, in a more recent study, in refractory individuals with primary obstetric APS, the inclusion of HCQ was linked to a greater rate of live births and a lower risk of pregnancy problems. [33] However, our results did not show a significant correlation between live birth rate and the use of HCQ. Nevertheless, there were 3 neonatal deaths reported in women with

autoimmune diseases- all of them, in pregnancies, whose mothers were not under HCQ, making it possible that the absence of a significant correlation, might be due to a small number of neonatal deaths.

Several articles, describe HCQ, as being linked to lower rates of PE. [2,13,15,16] PE is a serious complication for SLE patients and SLE pregnancies are at increased risk of developing it. [2,13] This condition lacks treatment options, possibly culminating in pregnancy termination. To avoid PE, the 2020 ACR recommendations advocate starting low-dose aspirin (81 or 100 mg daily) in the first trimester of SLE pregnancies. Nonetheless, there remains a scarcity of information. Immune response dysregulation and endothelial dysfunction are the primary causes of PE. To enhance the pathophysiological alterations in PE, HCQ can target numerous pathways. Rahman et al demonstrated that HCQ might diminish the production of TNF-a and endothelin-1, which impact endothelial dysfunction in PE, in an in vitro model. [50–52] A recent mouse research found that HCQ can protect against oxidative stress-induced endothelial damage and thereby enhance renal function by reducing NOX activity in SLE patients.[53,54] In vitro, TNF-a-induced human umbilical vein endothelial cell generation of 8-isoprostane and NOX expression were reduced by HCQ. [52] As a result, HCQ suppressed TNF-a, endothelin-1, and NOX activity, which had a strong protective effect on endothelial function. Based on these previous studies, HCQ may be an effective therapeutic for the prevention or treatment of PE in SLE. In individuals with SLE, HCQ should be given throughout pregnancy, regardless of disease activity. However, our findings are somewhat inconsistent with those reported, as there was no significant relation between the use of HCQ and HDP. Nonetheless, it should be noted that there were more cases of this conditions, reported in women who were not under HCQ, than the ones who were under HCQ. In addition, a recent meta-analysis by Liu et al, also showed no significant association between HCQ use and PE risk in lupus patients.[9]

Placental dysfunction induced by an increased risk of placental thrombosis in the context of an APS is hypothesized to be the cause of FGR in SLE pregnancies. It is thought that HCQ's antithrombotic activity may be essential in lowering low birth weight by improving placental vascularization. [31] In 118 SLE pregnancies, Leroux et al. found that maternal use of HCQ throughout pregnancy protected against PTD and FGR.[31] In addition, other studies are consistent with this findings.[2,16,34] However, Guillotin et al, found no impact on the prevention of FGR, with the use of HCQ, which was consistent with our findings. [30]

The association between prematurity and HCQ was also analysed. Women with SLE often have higher rates of pre-term deliveries, ranging from 19 to 49%, compared with 7% in the

general population. [31,55] Prematurity has been linked to an increased risk of respiratory distress syndrome, sepsis, intraventricular haemorrhage, hypoglycaemia, phototherapy-required jaundice, enterocolitis, more difficult breastfeeding, developmental delay, and school-related issues in children up to the age of five. Although several articles have shown a possible association, our study did not. [15,31] The recently documented favourable effects of antimalarials on endothelial dysfunction, which may sustain placental function and consequently pregnancy, might be one explanation for the prolonged pregnancy length in HCQ users. [36] However, our study was not the first to fail a relation. [30,36,38,39,56]

No significant differences were detected for other maternal outcomes such as HELLP Syndrome, GD and spontaneous abortion, low birth weight and Apgar score between the two groups, which was consistent with a recent meta-analysis. [15]

In fetuses exposed to maternal anti-Ro/SSA antibodies, HCQ may lessen the risk of CHB, especially in mothers who have already had a child with CHB. [57–60] However, our study failed to this association, because there were no sufficient cases of CHB, to make an association.

Although several articles, have demonstrated the benefits of HCQ in pregnancy and neonatal outcomes, in our study, HCQ did not significantly impact pregnancy outcomes. [15,16,31,33,34]. However, the absence of correlations, should be interpreted facing the multiple biases that might confound the results and conclusions, that this study contains. Firstly, this is a retrospective study, which contains a small number of cases analysed. Furthermore, variables such as early PTD, fetal deaths, GD, Gestational Hypertension, PE, FGR, low Apgar score, CHB, presence of anti-SSA/anti-SSB in newborn and SLE flares, did not include a significant number of cases to properly study the association.

On the other hand, this study contains 94 women with autoimmune diseases, whom might not have received uniform obstetric or rheumatological care. Then again, the precise dosage, duration of use and timing of HCQ during pregnancy is unknown and because HCQ is frequently dosed by weight, some women may have been underdosed, especially given their weight gain during pregnancy.[61] Furthermore, because our retrospective study did not consider adherence, it is possible that some women in the HCQ group did not actually take the medicine. Based on blood HCQ levels, 18%–44% of individuals with SLE who report using HCQ are not taking it outside of pregnancy. [62–65] A study published on the Journal of Rheumatology, evaluated HCQ levels throughout pregnancies and found that 24% of pregnant woman, within 25, showed very low HCQ levels, consistent with nonadherence. [66] Based on this previous research, we could estimate that a portion of women in our HCQ group, were non-adherent and so incorrectly

classified in the HCQ group. Considering that non-adherent women had the same rate of poor pregnancy outcomes as adherent women, the actual pregnancy outcomes for women taking HCQ, may be better than the data collected.

As described before, treatment with HCQ may have been correlated with more severe or active disease. Given that severe illness is linked to poorer outcomes, this form of confounding by indication would have skewed the results in favor of HCQ.

According to Alijotas-Reig et al. purely obstetric APS cases, may be a distinct subpopulation from thrombotic APS, with distinct pathogenic processes and risk factors.[67] This can be identified as another limitation of our study, because the distinction of obstetric APS was not made.

Other limitations to our study included missing information for certain pregnancies, and inability to examine disease activity before and throughout pregnancy, which is known to be highly associated with increased risk for maternal and/or fetal complications. Aside with disease activity, maternal characteristics such as BMI, socioeconomic position, parity, ethnicity, marital status, and cigarette use all have a significant influence on illness manifestation and fetal outcome. [35,68] Furthermore, our study group, included a high patient heterogeneity. In our study, most of these maternal traits were not precise or evaluated. In addition, It's crucial to stratify by parity to avoid a selection bias caused by negative outcomes in first pregnancies affecting the chance of future pregnancies.[13]

A group of healthy women was also compared to the study group. The age at conception was shown to have a strong association, indicating that healthy women are more likely to become pregnant sooner. Furthermore, healthy women have fewer past miscarriages and utilize fewer assisted reproductive technologies. When it came to GD, Gestational Hypertension, and FGR, however, there was no significant difference between the two groups, leading to the conclusion that HCQ had a protective impact on autoimmune disease patients, making their risks of unfavourable pregnancy outcomes almost comparable to healthy women.

CONCLUSION

In conclusion, while our data did not show that HCQ improved neonatal or maternal outcomes during SLE, APS, or SS pregnancy, it should be interpreted carefully and should not be used to discourage HCQ use in this context. In our study, autoimmune patients medicated with HCQ had a significative higher incidence of important risk factors for adverse obstetric outcomes. However, in our data this was not expressed in the perinatal outcomes. We could conclude that the use of HCQ was protective and that the absence of adverse outcomes in this group was a consequence of HCQ medication.

Advances in illness etiology and management knowledge have improved pregnancy outcomes for autoimmune disease patients. Given HCQ's excellent safety profile and a range of positive effects on obstetrical outcomes, it should be given to autoimmune disease patients prior to conception and maintained throughout pregnancy, regardless of disease activity, with potential benefits for both the mother and the infant.

TABLES

Table I: Demographic and Clinical Characteristics of Patients

Variable	Study Group (Patients with autoimmune disease who were taking HCQ)	Patients with Autoimmune diseases who were not taking HCQ	P value	Healthy group	P value
Age (years, mean ± SD)	33,11±5,244	33,2±5,060	0,934	30,75±5,733	<0,01
Obstetric History					
Nuliparity	21 (38,9%)	11 (27,5%)	0,249	96(44,7%)	
History of previous miscarriage	21 (38,9%)	19 (47,5%)	0,404	50 (23,3%)	0,02
ART pregnancy	5 (9,3%)	3 (7,5%)	0,762	3 (1,4%)	<0,01
Disease					
SLE	42 (77,8%)	10 (25%)		NA	
APS	4 (7,4%)	24 (60%)		NA	
SS	8 (14,8%)	6 (15%)		NA	
Age at diagnose (years, mean ± SD)	24,23±6,516	28,67±6,787	<0,01	NA	
Evolution time of disease before pregnancy (years, mean ± SD)	9,10±4,892	4,42±5,411	<0,01	NA	
Symptoms at conception	4 (7,4%)	4 (10%)			
Autoantibodies State					
ANA	45(83,3%)	17 (42,5%)	<0,01	NA	
Anti-dsDNA	20 (37%)	3 (7,5%)	<0,01	NA	
Anti-Ro/ SS-A	15 (27,8%)	6 (15%)	0,129	NA	
Anti-La/SS-B	5 (9,3%)	4 (10%)	0,904	NA	
Anti-cardiolipin	7 (13%)	26 (65%)	<0,01	NA	
Anti- β2 glycoprotein	9 (16,7%)	18 (45%)	<0,01	NA	
Lupus anticoagulant	3 (5,6%)	9 (22,5%)	<0,05	NA	
Complement decreased	10 (18,5%)	2 (5,0%)	<0,05	NA	
Medication before pregnancy					
HCQ	46 (85,2%)	1 (2,5%)	<0,01	NA	
ASA	19 (35,2)%)	17 (42,5%)	0,471	NA	
LMWH	7 (13,0%)	8 (20%)	0,357	NA	
Prednisone	17 (31,5%)	2 (5,0%)	<0,01	NA	
Cyclosporine	0	0		NA	
Medication during pregnancy					
HCQ	54 (100%)	0 (0%)		NA	
ASA	50 (92,6%)	37 (92,5%)	0,987	NA	
LMWH	29 (53,7%)	3 (7,5%)	0,11	NA	
Prednisone	20 (37%)	1 (2,5%)	<0,01	NA	
Azathioprine	5 (9,3%)	2 (5,0%)	0,437	NA	
Cyclosporine	2 (3,7%)	4 (10%)	0,396	NA	
Previous Comorbidities					
Chronic Arterial Hypertension	8 (14,8%)	8 (20%)	0,472	NA	
Lupus Nephritis	5 (9,3%)	0 (0%)	0,569	NA	
Flare < 6 months before pregnancy	1 (1,9%)	1 (2,5%)	0,351	NA	
Previous Gestacions					
Fetal Grownth Restritiction in previous gestations	0	3 (7,5%)			
Preeclampsia in previous gestation	1 (1,9%)	0 (0%)	0,444	NA	

ART, Assisted Reproductive Technology. SLE, Systemic Lupus Erythematosus. APS, Antiphospholipid Syndrome. SS, Sjogren's Syndrome. HCQ, Hydroxychloroquine. ASA, acetylsalicylic acid. LMWH- Low Molecular Weight Heparin.

Table II: Pregnancy Outcomes

Variable	Study Group (Patients with autoimmune disease who were taking HCQ)	Patients with Autoimmune diseases who were not taking HCQ	P value	Healthy group	P value
Live birth rate	54 (100%)	37 (92,1%)	0,089	215 (100%)	
Neonatal deaths	0	3 (7,5%)	0,089	0	
Mean gestacional age at delivery (weeks, mean ± SD)	37,91± 1,377	36,87±3,256	0,6	38,59±1,7	<0,01
Pre-term birth delivery	6 (11,1%)	10 (25%)	0,149	14 (6,5%)	0,08
Mode of Delivery					
Eutocic	14 (25,9%)	19 (47,5%)		127 (59,1%)	
C-section	20 (37%)	14 (35%)	0,839	72 (33,5%)	0,488
Distocic with forceps	3 (5,6%)	0		5 (2,3%)	
Distocic with suction cup	8 (14,8%)	5 (12,5%)		11 (5,1%)	
APO	27 (50%)	24 (60%)	0,336	37 (17,2%)	<0,001
Early Spontaneous Abortion	5 (9,3%)	1 (2,5%)	0,232	0	
Fetal deaths	2 (3,7%)	2 (5,0%	1	0	
Gestacional Diabetes	1 (1,9%)	5 (12,5%)	0,08	20 (9,3%)	0,093
Insuline Treatment	0	0		0	
Gestacional Hipertension	2 (3,7%)	4 (10%)	0,395	4 (1,9%)	0,376
Preeclampsia	1 (1,9%)	3 (7,5%)	0,309	0	0,966
Eclampsia	0	0		0	
HELLP Syndrome	0	0		0	
Fetal Grownth Restriction	3 (5,6%)	3 (7,5%)	1	7 (3,3%)	0,33
Cholestasis	1 (1,9%)	1 (2,5%)	1	NA	
Placenta praevia	1 (1,9%)	0	1	NA	
Aggravated symptoms with pregnancy	8 (15,1%)	3 (7,5%)	0,262	NA	

APO, Adverse Pregnancy Outcomes.

Table III: Neonatal outcomes

Variable	Study Group (Patients with autoimmune disease who were taking HCQ)	Patients with Autoimmune diseases who were not taking HCQ	P value	Healthy group	P Value
Average Newborn Weight (Grams, mean ± SD)	2902,73 ± 426,74	2763,03±751,365	0,296	3148,90±489,53	<0,01
Low birth weight (p<3)	4 (7,4%)	6 (15%)	0,238	NA	
Newborn sex					
Male	23 (51,1%)	20 (50%)		117 (54,4%)	
Female	22 (48,9%)			98 (45,6%)	
Mean Apgar Score					
1st minute	8,50±1,191	8,24±2,376	0,519	8,64±1,099	0,448
5th minute	9,59±0,693	9,21±2,315	0,302	9,71±0,664	0,282
Low Apgar Score					
1st minute	4 (7,41%)	4 (10%)	1	11 (10,3%)	0,523
5th minute	0	4 (10%)	<0,05	1 (0,5%)	
Neonatal complications	11(20,4%)	14 (35%)	0,19	34 (15,8%)	<0,01
Newborn ICU admission rate	4 (7,4%)	3 (7,5%)	1	3 (1,4%)	<0,01
CHB	2 (3,7%)	0	0,498	0	
Neonatal intervention and Pacemaker	2(100%)	0		0	
Newborn with anti-SSA/anti-SSB	5 (9,3%)	0%	0,149	0	

ICU, Intensive Care Unit. CHB, Congenital Heart Block.

Table IV: Maternal Outcomes

Variable	Study Group (Patients with autoimmune disease who were taking HCQ)	Patients with Autoimmune diseases who were not taking HCQ	P value	Healthy group
Maternal deaths	0	0		0
Diagnostic of Lupus during pregnancy	0	0		
Post-partum symptoms	7 (13%)	1 (2,5%)	0,131	NA
SLE flare during pregnancy	1 (1,9%)	0	1	NA
SLE flare post-partum	4 (7,4%)	1 (2,5%)	1	NA
Breastfeeding	35 (64,8%)	35 (97,2%)		NA

SLE, Systemic Lupus Erythematosus.

Table V: Data from all women with autoimmune diseases (patients who were taking HCQ+ patients who weren't taking HCQ)

	Patients with Autoimmune diseases
Age (years, mean ± SD)	33,15±5,139
Obstetric History	
Nuliparity	32 (34%)
History of previous miscarriage	40 (42,6%)
ART pregnancy	8 (8,5%)
Disease	
SLE	52
SAF	28
SS	14
Age at diagnose (years, mean ± SD)	26,05±6,945
Evolution time of disease before pregnancy (years, mean ± SD)	7,18 ± 5,582
Autoantibodies State	
ANA	62(66,7%)
Anti-dsDNA	23 (24,7%)
Anti-Ro/ SS-A	21 (22,6%)
Anti-La/SS-B	9 (9,6%)
Anti-cardiolipin	33 (36,3%)
Anti- β2 glycoprotein	27 (29%)
Lupus anticoagulant	12 (23%)
Complement decreased 1T	12 (12,9%)
Complement decresead 2T/3T	6(6,6%)
Medication before pregnancy	
HCQ	47 (50%)
ASA	36 (38,3%)
LMWH	15 (16%)
Prednisone	19 (20,2%)
Azathioprine	7 (7,4%)
Cyclosporine	0
Medication during pregnancy	
HCQ	54 (57,4%)
ASA	87 (92,6%)
LMWH	57 (60,6%)
Prednisone	21 (22,3%)
Azathioprine	7 (7,4%)
Cyclosporine	6 (6,4%)
Previous Comorbidities	
Chronic Arterial Hypertension	16 (17,2%)
Lupus Nephritis	5 (5,32%)
Flare < 6 months before pregnancy	2 (2,13%)
Previous Gestacions	
Preeclampsia in previous gestation	1 (1,07%)

	Patients with Autoimmune diseases
Live birth rate	91 (96,8%)
Neonatal deaths	3 (3,6%)
Mean gestacional age at delivery (weeks, mean ± SD)	37,5±2,4
Pre-term birth delivery	16 (19,5%)
Mode of Delivery	
Eutocic	33 (35,1%)
C-section	34 (36,2%)
Distocic with forceps	3 (3,2%)
Distocic with suction cup	13 (13,8%)
APO	
Early Spontaneous Abortion	6 (6,6%)
Fetal deaths	4 (4,4%)
Gestacional Diabetes	6 (6,7%)
Insuline Treatment	0
Gestacional Hipertension	6 (6,7%)
Preeclampsia	4 (4,5%)
Eclampsia	0
HELLP Syndrome	0
IUGR	6 (6,4%)
Cholestasis	2 (2,2%)
Placenta praevia	1 (1,1%)
Aggravated symptoms with pregnancy	11 (11,8%)
Average Newborn Weight (Grams, mean ± SD)	2837± 599,56
Low birth weight (p<3)	10 (10,6%)
Newborn sex	
Male	41(49,4%)
Female	42(50,6%)
Mean Apgar Score	
1^{st} minute	8,38
5^{th} minute	9,41
Low Apgar Score	
1^{st} minute	8
5^{th} minute	4 (4,9%)
Neonatal complications	25(30,5%)
Newborn ICU admission rate	7 (8,6%)
CHB	2
Neonatal intervention and Pacemaker replacement	2
Newborn with anti-SSA/anti-SSB	5 (7,5%)
Maternal deaths	0
Diagnostic of Lupus during pregnancy	0
Post-partum symptoms	8 (8,5%)
SLE flare during pregnancy	1 (1,1%)
SLE flare post-partum	5 (5,3%)
Breastfeeding	70 (74,5%)

ART, Assisted Reproductive Technology. SLE, Systemic Lupus Erythematosus. APS, Antiphospholipid Syndrome. SS, Sjogren's Syndrome. HCQ, Hydroxychloroquine. ASA, acetylsalicylic acid. LMWH- Low Molecular Weight Heparin. APO, Adverse Pregnancy Outcomes. ICU, Intensive Care Unit. CHB, Congenital Heart Block.

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