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Pregnancy in Patients with Sjögren's Syndrome

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

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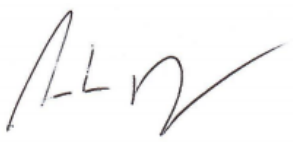
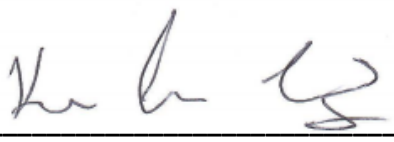
Orientador: 

Coorientador: 

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DEDICATÓRIA

À minha avó Helena, por tudo.

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RESUMO

Problema: Tem vindo a ser demonstrado que o Síndrome de Sjögren e a positividade para anti-SSA e/ou anti-SSB aumentam o risco de gravidezes complicadas. O nosso objetivo foi avaliar os desfechos maternos, fetais e neonatais em pacientes com estas características.

Métodos: Realizamos um estudo retrospetivo e comparamos mulheres grávidas da população obstétrica geral com três grupos de pacientes, entre 2015 e 2020: grávidas com Síndrome de Sjögren e positividade para anti-SSA e/ou anti-SSB; grávidas com Síndrome de Sjögren; e grávidas com positividade para anti-SSA e/ou anti-SSB.

Resultados: Um total de 143 mulheres foram incluídas. Relativamente a mulheres com Síndrome de Sjögren e positividade para anti-SSA e/ou anti-SSB (grupo 1), a idade média materna e ao diagnóstico foi de 34 e 29 anos, respetivamente. Em relação ao perfil de anticorpos, 80,2% apresentaram positividade para ANA, 70,6% para anti-SSA e 35,3% para anti-SSB. A doença autoimune concomitante mais frequente, para além do Síndrome de Sjögren, foi o lúpus eritematoso sistémico (41,2%); 38,2% eram primigestas; e 38,2% tiveram abortos espontâneos prévios. Sobre o recém-nascido, 58,8% eram do sexo masculino, 23,5% nasceram por cesariana, 8,8% foram diagnosticados com bloqueio cardíaco congénito, e 44,1% apresentaram positividade para anti-SSA. Comparando com os controlos, o grupo 1 apresentou uma taxa mais elevada de abortos espontâneos (17,6% *vs* 1,8%) (*P*=0,002), restrição de crescimento intrauterino (11,8% *vs* 0,9%) (*P*=0,005), partos pré-termo (14,7% *vs* 5,5%) (*P*=0,039), internamentos na unidade de cuidados intensivos neonatal (17,6% *vs* 0%) (*P*<0,001), e uma menor idade gestacional (38 *vs* 39 semanas) (*P*=0,023) e peso ao nascimento (2311 *vs* 3156 gramas) (*P*=0,019).

Conclusões: Mulheres com esta doença têm maior probabilidade de ter gravidezes complicadas, com piores desfechos fetais e neonatais.

Palavras-chave: Síndrome de Sjögren; Autoanticorpos; Gravidez; Recém-nascido.

ABSTRACT

Problem: Sjögren's Syndrome (SS) and anti-SSA and/or anti-SSB positivity have been shown to increase the risk of complicated pregnancies. Our goal was to evaluate maternal, fetal and neonatal outcomes in patients with these characteristics.

Method of Study: We performed a retrospective study and compared pregnant women of the general obstetrics population with three groups of patients, between 2015 and 2020: pregnant women with both SS and anti-SSA and/or anti-SSB positivity; pregnant women with SS; and pregnant women with anti-SSA and/or anti-SSB positivity.

Results: A total of 143 women were included. Regarding women with SS and/or anti-SSA and/or anti-SSB positivity (group 1), the mean maternal age at delivery and diagnosis was 34 and 29 years old, respectively. Concerning antibodies profile, 80.2% had ANA positivity, 70.6% had anti-SSA positivity and 35.3% had anti-SSB positivity. The most frequent concomitant autoimmune disorder, besides SS, was systemic lupus erythematosus (41.2%); 38.2% were primigravid; and 38.2% had previous spontaneous abortions. Regarding the newborn, 58.8% were male, 23.5% were delivered by cesarean, 8.8% had congenital heart block, and 44.1% had anti-SSA antibodies positivity. Compared to controls, group 1 had a higher rate of spontaneous abortions (17.6% vs 1.8%) (P=0.002), intrauterine growth restriction (11.8% vs 0.9%) (P=0.005), preterm deliveries (14.7% vs 5.5%) (P=0.039), admissions in the neonatal intensive care unit (17.6% vs 0%) (P<0.001), lower gestational age (38 vs 39 weeks) (P=0.023) and birthweight (2311 vs 3156 grams) (P=0.019).

Conclusion: Women with this disease are more likely to experience complicated pregnancies, with poorer fetal and neonatal outcomes.

Keywords: Sjögren's Syndrome; Autoantibodies; Pregnancy; Newborn.

LIST OF ABBREVIATIONS

SS – Sjögren's Syndrome

SLE – Systemic lupus erythematosus

NL – Neonatal lupus

CHUPorto – Centro Hospitalar Universitário do Porto

IUGR – Intrauterine growth restriction

ICU – Intensive care unit

MCTD – Mixed connective tissue disease

APS – Antiphospholipid antibody syndrome

DMARDs – Disease-modifying anti-rheumatic drugs

NSAIDs – Non-steroidal anti-inflammatory drugs

ANA – Antinuclear antibodies

ALT – Alanine aminotransferase

AST – Aspartate aminotransferase

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INTRODUCTION

Sjögren's Syndrome (SS) is a chronic multisystem autoimmune disorder characterized by inflammation and dysfunction of the exocrine glands, particularly the lacrimal and salivary glands, frequently resulting in xerophthalmia and xerostomia.[1,2] Additionally, there is a wide variety of extraglandular manifestations, as it can also affect several organ systems, namely the musculoskeletal, pulmonary, hepatic, renal and neurological.[3] This syndrome can present itself as primary, that is, isolated, or as secondary, associated with other autoimmune diseases, such as systemic lupus erythematosus (SLE).[1,3] SS has a much higher prevalence in females when compared to males, with a ratio of 9:1, and a peak incidence around the fourth decade of life, although it can present itself at any age.[2,4,5]

Additionally, SS is also characterized by the presence of a variety of antibodies, the most common being those directed against autoantigens SSA (RO) and SSB (La).[6] There is also a group of patients who have these antibodies, although not meeting the criteria required by the American College of Rheumatology/European League Against Rheumatism Classification Criteria for the diagnosis of SS.[7-9] During pregnancy, these antibodies can cross the placenta and may have several adverse effects on the fetus, and later on the newborn, namely neonatal lupus (NL).[10] Within the manifestations of NL, the most widely known and severe complication is congenital heart block.[6,8,10-12] Reports of pregnancy outcomes beyond neonatal lupus and congenital heart block are rare.[2,10]

It is known that autoimmune diseases can have a negative impact during pregnancy, both in pregnant women and newborns, depending on several factors, such as maternal disease activity, the severity of organ damage, antibody profile, drug treatment, among others.[13-15] There are several studies on the influence of other autoimmune diseases on pregnancy, such as SLE, showing a higher prevalence of poorer outcomes. However, few studies on maternal, fetal and neonatal outcomes in pregnant women diagnosed with SS.[13,15,16] On one hand, the low number of studies carried out regarding these topics may be related to the late clinical appearance of SS, as on the other hand, the recent increasing tendency of advanced maternal age at first pregnancy may explain the rising number of complicated pregnancies related to SS.[15] Among published studies, it has been shown that women with SS are more likely to develop pregnancy-related complications, such as an increased prevalence of spontaneous abortion or preterm deliveries, when compared to pregnant women without SS.[5,17]

Otherwise, study results on pregnancy outcomes of women with SS are few and conflicting, and no study was performed on the Portuguese population to this date. This study

aims to carry out a retrospective analysis to assess the possible maternal, fetal and neonatal outcomes in pregnant women diagnosed with SS or with the presence of anti-SSA and/or anti-SSB antibodies, although without criteria for SS diagnosis.

MATERIALS AND METHODS

This retrospective study was carried out at Centro Hospitalar Universitário do Porto (CHUPorto), in Oporto, Portugal. Ethical approval was granted by the institutional Ethics Committee (006-DEFI/006-CE), with access to the information recorded in the patients' electronic clinical files, accessed through *SClínico*® platform.

Inclusion criteria

The clinical records of three sample groups were analyzed: pregnant women of the general obstetric population, pregnant women diagnosed with Sjögren's Syndrome and pregnant women with antibodies against SSA (RO) and/or SSB (La) autoantigens, but without criteria for the diagnosis of Sjögren's Syndrome. The study cohort was divided into three groups of patients: women with SS and/or with anti-SSA/SSB antibodies positivity (group 1), women with SS (group 2) and women with anti-SSA antibodies positivity (group 3). Patient selection was based on a list of pregnant women with autoimmune disorders from the Maternal-Fetal Medicine Unit (UMMF), of CHUPorto, whose childbirth, stillbirth or abortion, spontaneous or voluntary, occurred between January 1st, 2015 and December 31th, 2020. We included three pregnant women that were followed in CHUPorto during pregnancy, however, as the fetus had been diagnosed with congenital heart block, they were transferred to Centro Hospitalar São João to give birth.

Data collection

Data was collected using *SClínico*® computer system, with data collection performed by anonymous registration. Regarding pregnant women, it was obtained information related to the sociodemographic profile, including age and weight; age at diagnosis of SS; laboratory analysis before and during pregnancy, as well as one month and six months after delivery or miscarriage; antibody and complement profile (C3 and C4) at conception and during pregnancy; treatment for SS at conception and during pregnancy; simultaneous presence of other autoimmune diseases or comorbidities, such as arterial hypertension. Obstetric data related to the actual gestation was collected, and information regarding previous gestations and births was also obtained. Considering the newborn, clinical data was collected, such as gestational age and weight at birth, gender; the presence of intrauterine growth restriction (IUGR) (birthweight <

10th percentile for age and sex); antibody profile; Apgar Score at one and five minutes[18]; the need for admission to a neonatal intensive care unit (ICU); diagnosis of neonatal lupus, including the presence of rash and congenital heart block; and perinatal mortality (stillbirth (>20 weeks of gestation) or neonatal death).

Regarding the obstetric data related to the pregnancy under study, it was analyzed the presence of comorbidities associated with pregnancy, namely gestational hypertension, eclampsia and preeclampsia; disease flare; type of labor; the presence of postpartum hemorrhage; termination of pregnancy, spontaneous abortion (<20 weeks of gestation); or maternal death. A disease flare was defined as the appearance and/or worsening of clinical manifestations that lead to a change in treatment strategy.

In relation to concomitant autoimmune diseases, systemic lupus erythematosus (SLE), mixed connective tissue disease (MCTD) and antiphospholipid antibody syndrome (APS) were highlighted.

With reference to the therapy carried out, both before and during pregnancy, we included prescription of glucocorticoids, hydroxychloroquine and other non-biological disease-modifying anti-rheumatic drugs (DMARDs), biological DMARDs, acetylsalicylic acid and heparin.

Concerning analytic data, the serum values of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and creatinine were considered. The maternal serum immunological profile analyzed included complement consumption before and during pregnancy, and the following antibodies: antinuclear antibodies (ANA), anti-SSA and anti-SSB. In the newborn, only the presence of anti-SSA and B antibodies were analyzed.

As diagnostic criteria for SS, the classification criteria proposed by the American College of Rheumatology/European League Against Rheumatism Consensus was used.[7,9]

Follow-up

The follow-up period was between the date of diagnosis of SS or SLE (for the eight patients with anti-SSA antibodies positivity, but without a SS diagnosis) and six months after delivery or abortion of the pregnancy under study, or until the date of data collection from the present study (March 10, 2021).

Statistical analysis

The statistical analysis was performed using the IBM SPSS Statistics® version 27.0.1. for Windows®. Categorical variables were described with frequency and percentage, and

continuous variables were expressed as mean and standard deviation (SD). The chi-square test and Fisher's exact test were used, as appropriate, to establish associations between categorical variables. Independent Samples T-Test was applied for continuous variables. A p-value of <0.05 was considered statistically significant.

RESULTS

This study analyzed 109 healthy pregnant women, without SS or anti-SSA/SSB antibodies (controls), and 34 pregnant women with Sjögren's Syndrome or with antibodies anti-SSA and/or anti-SSB, but without criteria for SS diagnosis, whose childbirth or abortion were between 2015 and 2020. Three comparison tables were designed: **Table V** comparing women with SS and/or with anti-SSA/SSB antibodies positivity (group 1) vs controls; **Table VI** comparing women with SS (group 2) vs controls; and **Table VII** comparing women with anti-SSA antibodies positivity (group 3) vs controls.

Baseline characteristics and clinical background of cases and controls are summarized in **Table I**. Considering group 1, the mean maternal age at delivery was 34 years old (SD 4.60), while the control group was 32 years old (SD 5.87). At the time of diagnosis, the mean maternal age was 29 years old (SD 7.46), and all women were diagnosed before the pregnancy at study. In relation to the clinical background, 38.2% and 31.2% of cases and controls, respectively, were primigravid. The rates of previous spontaneous abortions were 38.2% in cases and 25.7% in controls. Taking into consideration group 1, 76.5% had an established diagnosis of SS, 82.4% had ANA antibodies, 70.6% had anti-SSA antibodies and 35.3% had anti-SSB antibodies. The most frequent underlying autoimmune disease recorded in cases, besides SS, was SLE, in 41.2% of women (P<0.001). Regarding other autoimmune disorders in this group, 8.8% had APS (P=0.013) and 20.6% had APS antibodies present (P<0.001), 2.9% had MCTD and 35.3% had other autoimmune diseases (P<0.001). In controls, no women had SLE, APS or MCTD, and 1.8% had other autoimmune disorders. Of group 1, 5.9% had arterial hypertension, while this percentage was 1.8% in the control group. When analyzing C3 and/or C4 consumption in group 1, only 8.8% of those were decreased before pregnancy, while 11.8% were reduced during pregnancy. As described in **Table VIII**, hypocomplementemia (C3 and/or C4) was not associated with adverse obstetric outcomes.

Information related to the pregnancy at study is outlined in **Table II**. Among the 34 pregnancies in group 1 and 109 in the control group, rate of preeclampsia was 2.9% and 0.9%, respectively. No cases of eclampsia, gestational arterial hypertension, postpartum hemorrhage, maternal death, stillbirth, termination of pregnancy or disease flare were reported. However,

regarding spontaneous abortion, there was a higher rate of this event in women from group 1 when compared with those from the control group, with a percentage of 17.6% and 1.8%, respectively (*P*=0.002). The mean time between diagnosis and the pregnancy at study was six years (SD 3.64).

Of the therapy carried out directed to SS, described in **Table III**, within group 1, the percentage of use of glucocorticoids was 17.6%, hydroxychloroquine was 67.6% and other non-biological DMARDs was 14.7%, which they maintained during pregnancy. However, while only 20.6% were prescribed acetylsalicylic acid before pregnancy, this rate increased to 82.4% during pregnancy. In addition, 38.2% were prescribed with heparin during pregnancy. Of the women in the general obstetric population, 4.6% and 3.7% used glucocorticoids before and during pregnancy, respectively, and 5.5% were using acetylsalicylic acid before and during pregnancy. No woman of this group was prescribed with heparin, hydroxychloroquine or other non-biological DMARDs. Furthermore, no woman of both groups was prescribed with other NSAIDs, biological DMARDs, plasmapheresis, immunoglobulin or muscarinic agonists.

As presented in **Table IV**, when comparing newborns from controls vs group 1, the latter had higher rates of prematurity (14.7% vs 5.5%) (*P*=0.039), with a mean gestational age of 38 weeks (SD 1.48) vs 39 weeks (SD 1.82) (*P*=0.023), and IUGR (11.8% vs 0.9%) (*P*=0.005), with a mean weight at birth of 2311 grams (SD 501.05) vs 3156 grams (SD 463.86) (*P*=0.019). Regarding types of labor in group 1 and controls, 23.5% and 25.7% were born via caesarean, respectively, and 58.8% vs 45.9% were male (*P*=0.017). Only 5.9% in group 1 and 5.5% in the control group had an Apgar Score under seven at the first minute, and none had an under than seven score at the fifth minute. Regardless, in group 1, 17.6% of the newborn were admitted to the neonatal ICU, while none of the newborn of women in the general obstetric population was admitted (*P*<0.001). Considering group 1, 8.8% had congenital heart block (*P*=0.006), associated with NL, although no rash associated with this disease was reported. 44.1% had anti-SSA antibodies positivity.

Moreover, a comparison between patients with SS (group 2) (n=26) and controls (n=109) is reported in **Table VI**. Patients from group 2 had a higher rate of SLE (*P*<0.001) and presence of APS antibodies (*P*=0.001), although no women had APS itself, and a higher rate of other autoimmune disorders (*P*<0.001). In regard to antibodies profile, 80.8% of group 2 patients were ANA positive, 61.5% were anti-SSA positive and 46.2% were anti-SSB positive. Among these patients, 38.5% had primary SS and 61.5% had secondary SS. Mean maternal age was 34 years old (SD 4.90), while mean maternal age at diagnosis was 31 years old (SD 6.77) (with a mean

time between diagnosis and pregnancy of 5 years (SD 2.78)). Regarding previous and current pregnancy complications, in accordance with group 1, there was a significantly higher incidence of spontaneous abortion (*P*=0.003), although this is not seen in previous pregnancies (*P*=0.227), and no other significant difference was found. The rate of primigravid was 38.5%. In this comparison, in contrast to what was found when comparing group 1 vs controls, there was no significant difference between the prescription of glucocorticoids before and during pregnancy (*P*=0.143 and *P*=0.120, respectively), as well as the prescription of acetylsalicylic acid before pregnancy (*P*=0.194). Nevertheless, there was a significant difference regarding the prescription of acetylsalicylic acid during pregnancy (*P*<0.001), as well as heparin (*P*<0.001). With respect to hydroxychloroquine and non-biological DMARDs, there was a much higher prescription of these before and during pregnancy (hydroxychloroquine with a *P*<0.001 in both instances, and non-biological DMARDs with a *P*=0.005 and *P*=0.001, before and during pregnancy, respectively). Regarding the newborn, although there was no significant difference when analyzing birthweight, prematurity and gestational age, in group 2 there was higher prevalence of IUGR (11.5% vs 0.9%) (*P*=0.011), admission in the neonatal ICU (19.2% vs 0%) (*P*<0.001), congenital heart block (11.5% vs 0%) (*P*=0.003) and presence of anti-SSA antibodies (42.3% vs 0%) (*P*<0.001). As well as in group 1, there was a higher rate of male newborns (57.7% vs 45.9%) (*P*=0.027).

Finally, **Table VII** states the comparison between patients with anti-SSA antibodies positivity, regardless of SS diagnosis, (group 3) (n=24) and controls (n=109). In group 3, the mean maternal age was 33 years old (SD 4.48), while the mean maternal age at diagnosis of SS or SLE (in the eight patients that did not have a SS diagnosis) was 26 years old (SD 7.48). The mean time between diagnosis and pregnancy was eight years (SD 3.53). Regarding the antibody profile, these patients had 50.0% of anti-SSB positivity and 91.7% of ANA positivity. SS was diagnosed in 66.7% of these women, SLE in 50.0%, APS in 12.5% with APS antibodies present in 16.7%, and other autoimmune disorders in 12.5%. No woman was diagnosed with MCTD. In relation to arterial hypertension, the rate was of 8.3%. As well as in the other analyzed groups, there were no significant differences between this group and controls when evaluating rates of primigravids (41.7% in group 3) and previous spontaneous abortions (45.8% in group 3), as well as current pregnancy complications, except regarding rates of spontaneous abortion (16.7% vs 1.8% in controls) (*P*=0.010). With reference to the prescribed therapy, 25.0% were prescribed with glucocorticoids before and during pregnancy, 66.7% with hydroxychloroquine before pregnancy and 70.8% during pregnancy, 20.8% with non-biological DMARDs before pregnancy and 16.7% during pregnancy, 25.0% with acetylsalicylic acid before pregnancy and 83.3% during pregnancy,

and 41.7% with heparin during pregnancy. As well as what was found in the previous comparisons, there was a higher rate of males (58.3% vs 45.9% in controls) (*P*=0.087), prematurity (20.8% vs 5.5% in controls) (*P*=0.015) and IUGR (16.7% vs 0.9% in controls) (*P*=0.002), with a lower mean gestational age (38 weeks) (SD 1.50) (*P*=0.009) and birthweight (2831 grams) (SD 493.61) (*P*=0.002). Rates of caesarean delivery and Apgar Score did not differ between this group and controls. Furthermore, there was a higher rate of admission in the neonatal ICU (25.0% vs 0% in controls) (*P*<0.001), NL congenital heart block (12.5% vs 0% in controls) (*P*=0.003) and anti-SSA antibodies positivity (62.5% vs 0% in controls) (*P*<0.001).

DISCUSSION

This study showed that women with Sjögren's Syndrome and/or positivity for antibodies anti-SSA and/or anti-SSB had poorer pregnancy outcomes when compared to the general obstetric population included in the control group. Regarding clinical background, the rate of primigravid women and mean maternal age at the time of delivery did not differ from controls, in contrast to what was shown in other studies.[2,15] In relation to maternal age at the time of diagnosis, our sample showed a median age in the end of the third decade of life (29 years old), which is lower than what is stated in the literature.[2,4,5] However, as our sample only included pregnant women, it was expected a lower median age at diagnosis, considering that women diagnosed only in the fourth decade of life have fewer reproductive years left. As predicted, women in the study group had a significantly higher incidence of concomitant autoimmune disorders, such as SLE and APS, demonstrating that SS can present itself as secondary.[4]

When comparing both groups in terms of complications during pregnancy, such as the development of hypertensive events or rate of cesarean delivery, there was no significant difference from controls, in contrast to what was reported in other studies, that showed a higher rate of these events.[2,4,15] Furthermore, although rates of previous spontaneous abortions did not differ between group 1 and controls (*P*=0.193), group 1 reported a significantly higher incidence of spontaneous abortions in the current pregnancies, when compared with controls (*P*=0.002), showing that SS may affect the rate of spontaneous abortions, in agreement to what was found in some other studies.[15,16,19] Nevertheless, other studies did not establish this association.[2,4] As SS can present itself in combination with other autoimmune disorders, such as APS, and since APS carries a higher rate of spontaneous abortions, there was a possibility that the spontaneous abortions seen in our study were mainly caused by APS, rather than SS.[20,21] However, of the six women who had a spontaneous abortion in the current pregnancy (17.6%), five (83.3%) had primary SS and only one (16.6%) had secondary SS associated with APS. Also,

of the five women with primary SS, one (20%) had APS antibodies present, although not having an APS diagnosis. Therefore, the prevalence of spontaneous abortions in our sample does not seem to be associated with APS.

Regarding therapy choices for SS, these can range from muscarinic agonists, glucocorticoids, acetylsalicylic acid and other NSAIDs, hydroxychloroquine and other non-biological DMARDs, biological DMARDs, plasmapheresis or immunoglobulins.[1,22,23] In our sample, no patient was prescribed with biological DMARDs, immunoglobulin, muscarinic agonists or plasmapheresis. With reference to the therapy prescribed, it is relevant to realize that there was a significant increase in the prescription of acetylsalicylic acid, as well as a high rate of heparin prescription, during pregnancy. This fact can be explained since both acetylsalicylic acid and heparin were proven to decrease pregnancy-related complications, such as preeclampsia, preterm birth, IUGR and spontaneous abortion and thromboembolism.[24-26]

Furthermore, there were many significant differences between characteristics analyzed in newborns of group 1 and controls. In accordance to what was shown in other studies, in group 1 there was a higher rate of premature newborns and a lower mean gestational age.[2,4,15,17,27] Also, there was a higher rate of IUGR and a lower weight at birth.[2,4,17] It is curious that group 1 showed a higher rate of male newborns, when compared to controls (P=0.017). As expected, in group 1 there was a much higher rate of admission in the neonatal ICU (P<0.001), as well as congenital heart block (P=0.006) and presence of anti-SSA antibodies (P<0.001). This suggests that newborns from mothers with SS and/or anti-SSA/SSB antibodies have worse outcomes.[27]

It is noteworthy the high prevalence of congenital heart block, associated with NL, seen in cases, similar to what was reported by De Carolis et al.[15] When evaluating the three mothers and newborns (8.8%) with this diagnosis, only one of the mothers had SLE, in association with SS, and the other two mothers had primary SS. Furthermore, all of them were nulliparous and primigravid, except the women with SLE, who had a previous spontaneous abortion. All three newborns were diagnosed with a third-degree atrioventricular block during pregnancy, which carries a substantial case fatality rate and morbidity, and all of them required pacemaker implantation in the first days of life.[11,28] Additionally, one newborn had a preterm delivery at 36 weeks of gestation, while the two others were born full-term (37 and 39 weeks of gestation), although both with IUGR. All three were delivered by cesarean and all survived. As expected, all three mothers and newborns had anti-SSA antibodies positivity. In addition, all three women were prescribed with hydroxychloroquine before and during pregnancy, which seems to have

not protected congenital heart block occurrence, in contrast to what was shown in other studies.[28-32]

It is hypothesized that high disease activity, evaluated by disease flare and C3 and C4 hypocomplementemia, correlates with a worse maternal, fetal and neonatal outcome.[13,33-37] In group 1, no case of disease flare was reported. When evaluating complement consumption, namely C3 and/or C4, only 8.8% of women with the disease had hypocomplementemia before pregnancy, and only 11.8% had it during pregnancy, suggesting that most women had a low disease activity before and during pregnancy. When compared with women without hypocomplementemia, there was no significant difference in the prevalence of poorer outcomes.

Finally, when analyzing the comparison between patients with SS (group 2) vs controls and patients with anti-SSA/SSB antibodies (group 3) vs controls, the results suggest that there are only a few differences. In relation to baseline characteristics and clinical background, both compared groups had a significant difference regarding rate of concomitant autoimmune disorders, as expected, with the exception of MCTD. In relation to the current pregnancy at study, both groups had a significantly high rate of spontaneous abortion, which suggests that the presence of anti-SSA antibodies is itself a risk factor for this event, even without SS diagnosis. In relation to hydroxychloroquine prescription during pregnancy, 70.8% of patients with anti-SSA antibodies positivity (group 3) and 57.7% of patients with SS (group 2) were prescribed with it. Actually, as there are many more studies carried out about the relation between SLE and pregnancy outcomes, it was expected that these patients were more frequently prescribed with hydroxychloroquine, since many studies showed that this drug could prevent congenital heart block. However, this was not confirmed in the present study.[28-32] Regarding newborn outcomes, both groups maintained a significant statistical difference when evaluating rates of IUGR, admission in the neonatal ICU, congenital heart block and presence of anti-SSA antibodies. However, in contrast to patients of groups 1 and 3, patients with SS did not differ from controls when analyzing the rate of prematurity and mean gestational age and birthweight. This evidence suggests that both SS and anti-SSA antibodies positivity represent a risk factor for poorer newborn-related outcomes, and anti-SSA antibodies seem to carry a higher risk for preterm delivery, low gestational age and birthweight. Future studies exclusively regarding the influence of anti-SSA antibodies should be conducted, to further clarify these results.

A major limitation of this study was the fact that it is a single-center study with a small sample size, which is not representative of the national population. Furthermore, as this study

has a retrospective nature, data collection was limited, since the information reported in medical records is sometimes insufficient. Therefore, a larger multicenter prospective study should be conducted, in order to increase the validity of results, and, therefore, improve medical practice regarding Sjögren's Syndrome and presence of anti-SSA and/or anti-SSB antibodies.

CONCLUSION

Our study evaluated maternal, fetal and neonatal outcomes in patients with Sjögren's Syndrome and/or with anti-SSA and/or anti-SSB antibodies. As far as we are aware, this is the first Portuguese study on this subject. Compared to controls, in group 1 we reported a higher prevalence of spontaneous abortions, IUGR, preterm deliveries, admissions in the neonatal ICU, lower gestational age and birthweight. The most important finding in our study was the high prevalence of congenital heart block associated with neonatal lupus, even though all three cases were prescribed with hydroxychloroquine, which seems to have not protected this event from occurring. In conclusion, women with this disease are more likely to experience complicated pregnancies, with poorer fetal and neonatal outcomes. Close cooperation between women and their health care providers is necessary, with counseling about the possible complications that can occur, as well as the importance of vigilant surveillance. More investigation is needed to further understand the extent of Sjögren's Syndrome and anti-SSA and anti-SSB antibody implications on pregnancy.

Conflicts of Interest. The authors have no conflicts of interest to declare.

Author Contribution Statement. All authors were involved in drafting the article or revising it, and all authors approved the final version.

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APPENDICES

Table I: Demographic and clinical background characterization.

Variable	*Cases (n=34)*	*Control (n=109)*
Baseline characteristics – n(%)		
Maternal age (years) – Mean(SD)	34,09(4.60)	32.21(5.87)
Maternal age at diagnosis (years) – Mean(SD)	28.94(7.46)	-
Clinical background – n(%)		
ANA positive	28(82.4)	0(0)
Antibodies anti-SSA	24(70.6)	0(0)
Antibodies anti-SSB	12(35.3)	0(0)
Sjögren's Syndrome	26(76.5)	0(0)
Primary SS	10(38.5)	0(0)
Secondary SS	16(61.5)	0(0)
Arterial hypertension	2(5.9)	2(1.8)
SLE	14(41.2)	0(0)
MCTD	1(2.9)	0(0)
APS	3(8.8)	0(0)
APS antibodies	7(20.6)	0(0)
Other AI disorders	12(35.3)	2(1.8)
Decreased C3 and/or C4 pregestational	3(8.8)	0(0)
Primigravida	13(38.2)	34(31.2)
Previous spontaneous abortion	13(38.2)	28(25.7)

ANA: antinuclear antibodies; SS: Sjögren's Syndrome; SLE: systemic lupus erythematous; MCTD: mixed connective tissue disease; APS: antiphospholipid antibody syndrome; AI: autoimmune

Table II: Pregnancy outcomes characterization.

Variable	*Cases (n=34)*	*Control (n=109)*
During pregnancy – n(%)		
Time between diagnosis and pregnancy (years) – Mean(SD)	6.22(3.64)	-
Decreased C3 and/or C4	4(11.8)	0(0)
Abnormal AST	0(0)	0(0)
Abnormal ALT	0(0)	0(0)
Abnormal creatinine	1(2.9)	0(0)
Gestational arterial hypertension	0(0)	0(0)
Eclampsia	0(0)	0(0)
Preeclampsia	1(2.9)	1(0.9)
Disease flare	0(0)	-
Spontaneous abortion	6(17.6)	2(1.8)
Stillbirth	0(0)	0(0)
Termination of pregnancy	0(0)	0(0)
Postpartum hemorrhage	0(0)	0(0)
Maternal death	0(0)	0(0)

AST: aspartate aminotransferase; ALT: alanine aminotransferase; SS: Sjögren's Syndrome

Table III: Characterization of the therapy prescribed before and during pregnancy.

Variable	*Cases (n=34)*	*Control (n=109)*
Before pregnancy – n(%)		
Glucocorticoids	6(17.6)	5(4.6)
Hydroxychloroquine	23(67.6)	0(0)
Non-biological DMARDs	5(14.7)	0(0)
Acetylsalicylic acid	7(20.6)	6(5.5)
Other	0(0)	0(0)
During pregnancy – n(%)		
Glucocorticoids	6(17.6)	4(3.7)
Hydroxychloroquine	23(67.6)	0(0)
Non-biological DMARDs	5(14.7)	0(0)
Acetylsalicylic acid	28(82.4)	6(5.5)
Heparin	13(38.2)	0(0)
Other	0(0)	0(0)

DMARD: disease-modifying anti-rheumatic drugs

Table IV: Characterization of newborn outcomes.

Variable	*Cases (n=34)*	*Control (n=109)*
Newborn – n(%)		
Premature	5(14.7)	6(5.5)
Gestational age (weeks) – Mean(SD)	37.77(1.48)	38.65(1.82)
IUGR	4(11.8)	1(0.9)
Caesarean	8(23.5)	28(25.7)
Male gender	20(58.8)	50(45.9)
Weight at birth (grams) – Mean(SD)	2311.35(501.05)	3155.79(463.86)
Apgar 1 minute < 7	2(5.9)	6(5.5)
Apgar 5 minutes < 7	0(0)	0(0)
Neonatal ICU	6(17.6)	0(0)
NL rash	0(0)	0(0)
NL congenital heart block	3(8.8)	0(0)
Antibodies anti-SSA	15(44.1)	0(0)

IUGR: intrauterine growth restriction; ICU: intensive care unit; NL: neonatal lupus

Table V: Comparison between women with SS and/or with anti-SSA/SSB antibodies positivity (group 1) and controls.

		Sjögren's Syndrome and/or antibodies anti-SSA		
	Total (n=143)	Yes (n=34)	No (n=109)	*P*
Maternal				
Baseline characteristics – n(%)				
Maternal age (years) – Mean(SD)	32.66(5.64)	34,09(4.60)	32.21(5.87)	0.057
Maternal age at diagnosis (years) – Mean(SD)	28.94(7.46)	28.94(7.46)	-	-
Clinical background – n(%)				
ANA positive	28(13.9)	28(82.4)	0(0)	-
Antibodies anti-SSA	24(11.9)	24(70.6)	0(0)	<0.001
Antibodies anti-SSB	12(6.0)	12(35.3)	0(0)	<0.001
Sjögren's Syndrome	26(12.9)	26(76.5)	0(0)	<0.001
Primary SS	10(5.0)	10(29.4)	0(0)	<0.001
Secondary SS	16(8.0)	16(47.1)	0(0)	<0.001
Arterial hypertension	4(2.0)	2(5.9)	2(1.8)	0.242
SLE	14(7.0)	14(41.2)	0(0)	<0.001
MCTD	1(0.5)	1(2.9)	0(0)	0.238
APS	3(1.5)	3(8.8)	0(0)	0.013
APS antibodies	7(3.5)	7(20.6)	0(0)	<0.001
Other AI disorders	14(7.0)	12(35.3)	2(1.8)	<0.001
Decreased C3 and/or C4 pregestational	3(1.5)	3(8.8)	0(0)	-
Primigravida	47(23.4)	13(38.2)	34(31.2)	0.531
Previous spontaneous abortion	41(20.4)	13(38.2)	28(25.7)	0.193
During pregnancy – n(%)				
Time between diagnosis and pregnancy (years) – Mean(SD)	6.22(3.64)	6.22(3.64)	-	-
Decreased C3 and/or C4	4(2.0)	4(11.8)	0(0)	-
Abnormal AST	0(0)	0(0)	0(0)	-
Abnormal ALT	0(0)	0(0)	0(0)	-
Abnormal creatinine	1(0.5)	1(2.9)	0(0)	-
Gestational arterial hypertension	0(0)	0(0)	0(0)	-
Eclampsia	0(0)	0(0)	0(0)	-
Preeclampsia	2(1.0)	1(2.9)	1(0.9)	0.417
Disease flare	0(0)	0(0)	-	-
Spontaneous abortion	8(4.0)	6(17.6)	2(1.8)	0.002
Stillbirth	0(0)	0(0)	0(0)	-
Termination of pregnancy	0(0)	0(0)	0(0)	-
Postpartum hemorrhage	0(0)	0(0)	0(0)	-
Maternal death	0(0)	0(0)	0(0)	-
Therapy – n(%)				
Before pregnancy				
Glucocorticoids	11(5.5)	6(17.6)	5(4.6)	0.015
Hydroxychloroquine	23(11.4)	23(67.6)	0(0)	<0.001
Non-biological DMARDs	5(2.5)	5(14.7)	0(0)	<0.001
Acetylsalicylic acid	13(6.5)	7(20.6)	6(5.5)	0.009
Other	0(0)	0(0)	0(0)	-
During pregnancy				
Glucocorticoids	10(5.0)	6(17.6)	4(3.7)	0.011
Hydroxychloroquine	23(11.4)	23(67.6)	0(0)	<0.001
Non-biological DMARDs	5(2.5)	5(17.4)	0(0)	<0.001
Acetylsalicylic acid	34(16.9)	28(82.4)	6(5.5)	<0.001

Heparin	13(6.5)	13(38.2)	0(0)	<0.001
Other	0(0)	0(0)	0(0)	-
Newborn – n(%)				
Premature	11(5.5)	5(14.7)	6(5.5)	0.039
Gestational age (weeks) – Mean(SD)	38.48(1.79)	37.77(1.48)	38.65(1.82)	0.023
IUGR	5(2.5)	4(11.8)	1(0.9)	0.005
Caesarean	36(17.9)	8(23.5)	28(25.7)	0.630
Male gender	70(34.8)	20(58.8)	50(45.9)	0.017
Weight at birth (grams) – Mean(SD)	3108.01(479.37)	2311.35(501.05)	3155.79(463.86)	0.019
Apgar 1 minute < 7	8(4.0)	2(5.9)	6(5.5)	0.646
Apgar 5 minutes < 7	0(0)	0(0)	0(0)	-
Neonatal ICU	6(3.0)	6(17.6)	0(0)	<0.001
NL rash	0(0)	0(0)	0(0)	-
NL congenital heart block	3(1.5)	3(8.8)	0(0)	0.006
Antibodies anti-SSA	15(7.5)	15(44.1)	0(0)	<0.001

ANA: antinuclear antibodies; SS: Sjögren's Syndrome; SLE: systemic lupus erythematous; MCTD: mixed connective tissue disease; APS: antiphospholipid antibody syndrome; AI: autoimmune**;** AST: aspartate aminotransferase; ALT: alanine aminotransferase; DMARD: disease-modifying anti-rheumatic drugs**;** IUGR: intrauterine growth restriction; ICU: intensive care unit; NL: neonatal lupus

Table VI: Comparison between women with SS (group 2) and controls.

		Sjögren's Syndrome		
	Total (n=135)	Yes (n=26)	No (n=109)	*P*
Maternal				
Baseline characteristics – n(%)				
Maternal age (years) – Mean(SD)	32.56(5.72)	34.04(4.90)	32.21(5.87)	0.144
Maternal age at diagnosis (years) – Mean(SD)	31.46(6.77)	31.46(6.77)	-	-
Clinical background – n(%)				
ANA positive	21(15.6)	21(80.8)	0(0)	-
Antibodies anti-SSA	16(11.9)	16(61.5)	0(0)	<0.001
Antibodies anti-SSB	12(8.9)	12(46.2)	0(0)	<0.001
Sjögren's Syndrome	26(19.3)	26(100.0)	0(0)	-
Primary SS	10(7.4)	10(38.5)	0(0)	<0.001
Secondary SS	16(11.9)	16(61.5)	0(0)	<0.001
Arterial hypertension	2(1.5)	0(0)	2(1.8)	1.000
SLE	6(4.4)	6(23.1)	0(0)	<0.001
MCTD	1(0.7)	1(3.8)	0(0)	0.193
APS	0(0)	0(0)	0(0)	-
APS antibodies	4(3.0)	4(15.4)	0(0)	0.001
Other AI disorders	14(10.4)	12(46.2)	2(1.8)	<0.001
Decreased C3 and/or C4 pregestational	3(2.2)	3(11.5)	0(0)	-
Primigravida	44(32.6)	10(38.5)	34(31.2)	0.492
Previous spontaneous abortion	38(28.1)	10(38.5)	28(25.7)	0.227
During pregnancy – n(%)				
Time between diagnosis and pregnancy (years) – Mean(SD)	4.92(2.78)	4.92(2.78)	-	-
Decreased C3 and/or C4	4(3.0)	4(15.4)	0(0)	-
Abnormal AST	0(0)	0(0)	0(0)	-
Abnormal ALT	0(0)	0(0)	0(0)	-
Abnormal creatinine	0(0)	0(0)	0(0)	-
Gestational arterial hypertension	0(0)	0(0)	0(0)	-
Eclampsia	0(0)	0(0)	0(0)	-
Preeclampsia	1(0.7)	0(0)	1(0.9)	1.000
Disease flare	0(0)	0(0)	-	-
Stillbirth	0(0)	0(0)	0(0)	-
Termination of pregnancy	0(0)	0(0)	0(0)	-
Spontaneous abortion	7(5.2)	5(19.2)	2(1.8)	0.003
Postpartum hemorrhage	0(0)	0(0)	0(0)	-
Maternal death	0(0)	0(0)	0(0)	-
Therapy – n(%)				
Before pregnancy				
Glucocorticoids	8(5.9)	3(11.5)	5(4.6)	0.143
Hydroxychloroquine	16(11.9)	16(61.5)	0(0)	<0.001
Non-biological DMARDs	3(2.2)	3(11.5)	0(0)	0.005
Acetylsalicylic acid	9(6.7)	3(11.5)	6(5.5)	0.194
Other	0(0)	0(0)	0(0)	-
During pregnancy				
Glucocorticoids	7(5.2)	3(11.5)	4(3.7)	0.120
Hydroxychloroquine	15(11.1)	15(57.7)	0(0)	<0.001
Non-biological DMARDs	4(3.0)	4(15.4)	0(0)	0.001
Acetylsalicylic acid	27(20.0)	21(80.8)	6(5.5)	<0.001
Heparin	8(5.9)	8(30.8)	0(0)	<0.001

Other	0(0)	0(0)	0(0)	-
Newborn – n(%)				
Premature	8(5.9)	2(7.7)	6(5.5)	0.346
Gestational age (weeks) – Mean(SD)	38.56(1.76)	38.05(1.27)	38.65(1.82)	0.171
IUGR	4(3.0)	3(11.5)	1(0.9)	0.011
Caesarean	34(25.2)	6(23.1)	28(25.7)	0.588
Male gender	65(48.1)	15(57.7)	50(45.9)	0.027
Weight at birth (grams) – Mean(SD)	3132.02(468.94)	2998.16(487.65)	3155.79(463.86)	0.178
Apgar 1 minute < 7	7(5.2)	1(3.8)	6(5.5)	1.000
Apgar 5 minutes < 7	0(0)	0(0)	0(0)	-
Neonatal ICU	5(3.7)	5(19.2)	0(0)	<0.001
NL rash	0(0)	0(0)	0(0)	-
NL congenital heart block	3(2.2)	3(11.5)	0(0)	0.003
Antibodies anti-SSA	11(8.1)	11(42.3)	0(0)	<0.001

ANA: antinuclear antibodies; SS: Sjögren's Syndrome; SLE: systemic lupus erythematous; MCTD: mixed connective tissue disease; APS: antiphospholipid antibody syndrome; AI: autoimmune**;** AST: aspartate aminotransferase; ALT: alanine aminotransferase; DMARD: disease-modifying anti-rheumatic drugs**;** IUGR: intrauterine growth restriction; ICU: intensive care unit; NL: neonatal lupus

Table VII: Comparison between women with anti-SSA antibodies positivity (group 3) vs controls.

		Antibodies anti-SSA		
	Total (n=133)	Yes (n=24)	No (n=109)	*P*
Maternal				
Baseline characteristics – n(%)				
Maternal age (years) – Mean(SD)	32.44(5.64)	33.44(4.48)	32.21(5.87)	0.115
Maternal age at diagnosis (years) – Mean(SD)	26.20(7.48)	26.20(7.48)	-	-
Clinical background – n(%)				
ANA positive	22(16.4)	22(91.7)	0(0)	-
Antibodies anti-SSA	24(17.9)	24(100.0)	0(0)	<0.001
Antibodies anti-SSB	12(9.0)	12(50.0)	0(0)	<0.001
Sjögren's Syndrome	17(12.7)	16(66.7)	0(0)	<0.001
Primary SS	9(6.7)	9(37.5)	0(0)	<0.001
Secondary SS	8(6.0)	7(29.2)	0(0)	<0.001
Arterial hypertension	4(3.0)	2(8.3)	2(1.8)	0.151
SLE	12(9.0)	12(50.0)	0(0)	<0.001
MCTD	0(0)	0(0)	0(0)	-
APS	3(2.2)	3(12.5)	0(0)	0.005
APS antibodies	5(3.7)	4(16.7)	0(0)	0.008
Other AI disorders	6(4.5)	3(12.5)	2(1.8)	0.041
Decreased C3 and/or C4 pregestational	2(1.5)	2(8.3)	0(0)	-
Primigravida	45(33.6)	10(41.7)	34(31.2)	0.345
Previous spontaneous abortion	39(29.1)	11(45.8)	28(25.7)	0.081
During pregnancy – n(%)				
Time between diagnosis and pregnancy (years) – Mean(SD)	8.00(3.53)	8.00(3.53)	-	0.015
Decreased C3 and/or C4	3(2.2)	3(12.5)	0(0)	-
Abnormal AST	0(0)	0(0)	0(0)	-
Abnormal ALT	0(0)	0(0)	0(0)	-
Abnormal creatinine	1(0.7)	1(4.2)	0(0)	-
Gestational arterial hypertension	0(0)	0(0)	0(0)	-
Eclampsia	0(0)	0(0)	0(0)	-
Preeclampsia	2(1.5)	1(4.2)	1(0.9)	0.334
Disease flare	0(0)	0(0)	-	-
Spontaneous abortion	6(4.5)	4(16.7)	2(1.8)	0.010
Stillbirth	0(0)	0(0)	0(0)	-
Termination of pregnancy	0(0)	0(0)	0(0)	-
Postpartum hemorrhage	0(0)	0(0)	0(0)	-
Maternal death	0(0)	0(0)	0(0)	-
Therapy – n(%)				
Before pregnancy				
Glucocorticoids	11(8.2)	6(25.0)	5(4.6)	0.002
Hydroxychloroquine	16(11.9)	16(66.7)	0(0)	<0.001
Non-biological DMARDs	5(3.7)	5(20.8)	0(0)	<0.001
Acetylsalicylic acid	12(9.0)	6(25.0)	6(5.5)	0.005
Other	0(0)	0(0)	0(0)	-
During pregnancy				
Glucocorticoids	10(7.5)	6(25.0)	4(3.7)	0.002
Hydroxychloroquine	17(12.7)	17(70.8)	0(0)	<0.001
Non-biological DMARDs	4(3.0)	4(16.7)	0(0)	<0.001
Acetylsalicylic acid	27(20.1)	20(83.3)	6(5.5)	<0.001
Heparin	11(8.2)	10(41.7)	0(0)	<0.001

Other	0(0)	0(0)	0(0)	-
Newborn – n(%)				
Premature	11(8.2)	5(20.8)	6(5.5)	0.015
Gestational age (weeks) – Mean(SD)	38.48(1.81)	37.50(1.50)	38.65(1.82)	0.009
IUGR	5(3.7)	4(16.7)	1(0.9)	0.002
Caesarean	36(26.9)	8(33.3)	28(25.7)	0.279
Male gender	65(48.5)	14(58.3)	50(45.9)	0.087
Weight at birth (grams) – Mean(SD)	3102.54(482.20)	2831.19(493.62)	3155.79(463.86)	0.002
Apgar 1 minute < 7	8(6.0)	2(8.3)	6(5.5)	0.346
Apgar 5 minutes < 7	0(0)	0(0)	0(0)	-
Neonatal ICU	6(4.5)	6(25.0)	0(0)	<0.001
NL rash	0(0)	0(0)	0(0)	-
NL congenital heart block	3(2.2)	3(12.5)	0(0)	0.003
Antibodies anti-SSA	15(11.2)	15(62.5)	0(0)	<0.001

ANA: antinuclear antibodies; SS: Sjögren's Syndrome; SLE: systemic lupus erythematous; MCTD: mixed connective tissue disease; APS: antiphospholipid antibody syndrome; AI: autoimmune**;** AST: aspartate aminotransferase; ALT: alanine aminotransferase; DMARD: disease-modifying anti-rheumatic drugs**;** IUGR: intrauterine growth restriction; ICU: intensive care unit; NL: neonatal lupus

Table VIII: Comparison of pregnancy and newborn related complications, between women of group 1 with hypocomplementemia and women of group 1 without hypocomplementemia.

		Decreased C3 and/or C4		
	Total (n=34)	Yes (n=5)	No (n=29)	*P*
Maternal				
During pregnancy – n(%)				
Gestational arterial hypertension	0(0)	0(0)	0(0)	-
Eclampsia	0(0)	0(0)	0(0)	-
Preeclampsia	1(2.9)	0(0)	1(3.4)	1.000
Disease flare	0(0)	0(0)	0(0)	
Spontaneous abortion	6(17.6)	0(0)	6(20.7)	0.559
Stillbirth	0(0)	0(0)	0(0)	-
Termination of pregnancy	0(0)	0(0)	0(0)	-
Postpartum hemorrhage	0(0)	0(0)	0(0)	-
Maternal death	0(0)	0(0)	0(0)	-
Newborn – n(%)				
Premature	5(14.7)	0(0)	5(17.2)	0.555
Gestational age (weeks) – Mean(SD)	37.77(1.48)	38.25(0.96)	37.68(1.56)	0.491
IUGR	4(11.8)	1(20.0)	3(10.3)	0.511
Cesarean	8(23.5)	1(20.0)	7(24.1)	0.641
Weight at birth (grams) – Mean(SD)	2311.35(501.05)	2963.75(398.57)	3950.00(2901.82)	0.825
Apgar 1 minute < 7	2(5.9)	0(0)	2(6.9)	1.000
Apgar 5 minutes < 7	0(0)	0(0)	0(0)	-
Neonatal ICU	6(17.6)	2(40.0)	4(13.8)	0.218
NL rash	0(0)	0(0)	0(0)	-
NL congenital heart block	3(8.8)	1(20.0)	2(6.9)	0.422
Antibodies anti-SSA	15(44.1)	3(60.0)	12(41.4)	1.000

IUGR: intrauterine growth restriction; ICU: intensive care unit; NL: neonatal lupus

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centro hospitalar do Porto

Exma. Sra. Maria Inês Abreu

Estudante do ICBAS

ASSUNTO: Trabalho Académico - MIM - **"Gravidez em Doentes com Síndrome de Sjögren"** – N/ REF.ª 2021.007(006-DEFI/006-CE)

O Conselho de Administração do CHUP autoriza a realização do estudo acima mencionado, a realizar no Serviço de Obstetrícia desta Instituição e tendo como Investigador Principal Maria Inês Abreu, estudante do ICBAS.

O estudo foi previamente analisado pela Comissão de Ética do CHUP|ICBAS, pelo Serviço de Investigação Clínica, pela Direção do Departamento de Ensino, Formação e Investigação do CHUP e pelo Presidente do Conselho de Administração, tendo obtido parecer favorável.

Cumprimentos,

CONSELHO DE ADMINISTRAÇÃO
13/2/2021

Dr. PAULO BARBOSA — Presidente

Dr.ª RITA MOREIRA — Vogal Executiva

Prof. Doutor JOSÉ BARROS — Diretor Clínico

Dr.ª RITA VELOSO — Vogal Executiva

Enf.º EDUARDO ALVES — Enfermeiro Diretor

* Em todas as eventuais comunicações posteriores sobre este estudo é indispensável indicar a nossa ref.ª.