A narrative review about the association between Sjögren's syndrome and pregnancy

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Abstract

Sjögren syndrome (SS) is one of the most frequently autoimmune systemic diseases that may influence pregnancy outcome, and pregnancy may influence its evolution. SS increases the risk of fetal complications, including neonatal lupus and congenital heart diseases, and even causes loss of pregnancy. In this article, we provide a review of particularities of SS during pregnancy and the recommended management. The gestation period is contraindicated for most antirheumatic drugs, and there is an overexpression of symptoms and a higher risk of associated complications. Therefore, every woman should have an antenatal management to effectively control the basic pathology, and to be explained in detail the risks that can occur in case of a pregnancy both for her and for the conception product. If the pregnant woman's state deteriorates or in case of fetal complications, there are a series of therapies that can be used which provide more or less effective solutions. In conclusion, Sjögren's syndrome remains difficult to diagnose during pregnancy and challenging to manage when diagnosed.

Keywords: *Sjögren syndrome, pregnancy, antinuclear antibodies, SS-A antibodies (anti-Ro), SS-B antibodies (anti-LA), congenital neonatal lupus*

Rezumat

Sindromul Sjögren (SS) este una dintre cele mai frecvente boli sistemice autoimune care poate influența rezultatul sarcinii, iar sarcina poate influența evoluția acesteia. SS crește riscul de complicații fetale, inclusiv riscul de apariție a lupusului neonatal și a bolilor cardiace congenitale, și poate provoca chiar pierderea sarcinii. În acest articol, oferim o trecere în revistă a particularităților SS în timpul sarcinii și a managementului recomandat. Majoritatea medicamentelor antireumatice sunt contraindicate în sarcină, deoarece există o manifestare mai puternică a simptomelor și un risc mai mare de complicații asociate. De aceea, fiecărei femei i se recomandă să aibă un management prenatal pentru a controla eficient patologia de bază și să i se explice în detaliu riscurile care pot apărea în cazul unei sarcini, atât pentru produsul de concepție, cât și pentru ea. Dacă starea gravidei se deteriorează sau dacă apar complicații fetale, există o serie de terapii care pot fi folosite și care oferă soluții mai mult sau mai puțin eficiente. În concluzie, sindromul Sjögren rămâne dificil de diagnosticat în timpul sarcinii și greu de gestionat atunci când este diagnosticat.

Cuvinte-cheie: *sindromul Sjögren, sarcină, anticorpii antinucleari, anticorpi anti-SS-A (anti-Ro), anticorpi anti-SS-B (anti-La), lupus neonatal congenital*

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Introduction

Sjögren syndrome (SS, SHOW-grins syndrome) is one of the most frequently autoimmune diseases, that can be found at any age, although it has a predilection for around the age of 40. SS is manifested by reduced or absent salivary or lacrimal gland secretion due to lymphocytic infiltration of this exocrine glands and organs[(1)]. Since 2017, the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) have validated specific criteria for the correct classification of primary Sjögren's syndrome (pSS)[(1)]. These criteria target individuals with clinical signs/symptoms suggestive of SS. The prevalence of Sjögren's syndrome is between 0.1% and 4.8%[(2)], mainly affecting the female sex (9:1 female-male ratio)[(3)]. Considering the current trends of having the first pregnancy at an older age than 20 years ago, the age range preferred for conception overlaps with the age range when Sjögren's syndrome has the highest incidence[(4)].

Sjögren's syndrome is an autoimmune multisystemic disease that may be present alone, as primary Sjögren's syndrome, or in association with other rheumatic connective tissue diseases, such as rheumatoid arthritis or systemic lupus erythematosus, in which case it is secondary Sjögren's syndrome[(5)].

The defining histological characteristics of this pathology are focal lymphocytic infiltration of the exocrine glands. The specific markers are: antinuclear antibodies, anti SS-A (anti-Ro), anti SS-B (anti-La), cryoglobulins and hypocomplementemia[(6)]. These markers are the main cause of complications encountered in pregnant women with Sjögren's syndrome, as they are able to cross

the fetoplacental barrier around the age of 11-12 weeks of gestation. Their effect on fetal tissues can be: the production of arrhythmias, myocarditis, or the blocking of physiological clearance by binding to apoptotic cells[7,8].

However, there is limited information on the effect of pregnancy on primary Sjögren's syndrome, while the association with systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS) is much better known.

Prenatal management

Women diagnosed with Sjögren's syndrome should be provided with information about all the possible risks of pregnancy in their case. Most medications used in the management of rheumatological pathologies are contraindicated during pregnancy. Because of this, patients are advised to think about conception only after 3-6 months of an effective control of the disease[4].

All positive anti-SSA/Ro pregnant women – especially those with previous babies with congenital heart block – must be treated with hydroxychloroquine (5 mg/kg/d)[9] in order to prevent heart block and cutaneous manifestations[10]. In case of previously affected pregnancies, the risk of cardiac neonatal lupus was calculated as being approximately 2%[11,12], but at 1-18% after a previous affected child[13].

Hydroxychloroquine is considered safe during pregnancy, many authors showing that the benefits outweigh the risks[14]. Hydroxychloroquine was associated with retinal and auditory side effects, but from reports from more than 40 years ago[15].

Pregnancy causes a worsening of the symptoms for Sjögren's syndrome, both during pregnancy and postpartum. In general, pulmonary hypertension is exacerbated and should be monitored carefully. In addition, Sjögren's syndrome increases the occurrence of complications during pregnancy. In this case, the effect of secondary Sjögren's syndrome are better known.

All of these aspects must be explained to women who a desire a pregnancy, understood and integrated into a multidisciplinary therapeutic plan.

Antenatal management

Congenital heart block is the most significant and studied complicated concerns of pregnancies with Sjögren's syndrome, being a manifestation of neonatal lupus, with extremely high morbidity and mortality. Since the pathophysiological basis of this disease of the newborn is the transplacental transfer of anti-Ro antibodies (SSA) and/or anti-La (SSB), the risk of the newborn to develop this pathology increases as the titer of anti SS-A antibodies becomes higher in pregnant women. Anti SS-A antibodies may cross-react with T- and L-type calcium channels[8,16] and, thus, specific immune-mediated destruction of the atrioventricular node occurs. Neonatal lupus is not a common pathology, being only present in 1-2% of newborns from mothers with autoimmune diseases, including Sjögren's syndrome[11]. However, this percentage increases to 20% if the woman has given birth to a child with neonatal or congenital heart block before[17].

Thus, it is mandatory to follow-up using weekly echocardiograms, especially between 16 and 20 weeks, and electrocardiogram, in order to be able to make an early diagnosis of possible cases of congenital heart block (CHB)[9].

Electrocardiogram disorders are manifested as QT interval prolongation, sinus bradycardia, or atrioventricular nodal dysfunction[18].

In addition to early diagnosis, medical treatment and pacemaker should be decided as soon as possible in cases of incomplete congenital heart block or recent congenital heart block[19].

There are two purposes of treatment: on the one hand, to decrease the antibodies in the maternal blood and, on the other hand, to decrease the inflammation before it reaches the stage of fibrosis and causes irreversible congenital heart block[20].

Dexamethasone or betamethasone can be given to reduce the inflammatory response that leads to the destruction of nodal tissue. Since these treatments are not degraded by placental hydroxylase, they can be used during pregnancy[21].

However, if the treatment is not initiated in time, there is no study in which dexamethasone shows a reversible effect on CHB[21-23], but only on carditis or incomplete CHB, as well as on fetal hemodynamics[19,21-25].

Alternatively, corticosteroid treatment also comes with well-known side effects: infection, osteonecrosis, osteoporosis[26,27].

The newborn may also present neonatal lupus syndrome[8], manifested as life-threatening cardiac anomalies, liver abnormalities, rash, thrombocytopenia[28], or even autoimmune hemolytic anemia[29], which are directly related to the high titer of anti SS-A antibodies. In addition to congenital heart block, maternal Sjögren's syndrome can also cause spontaneous abortion, stillbirth, neonatal death, intrauterine growth restriction, premature birth, oligohydramnios, adrenal suppression and small for gestational age[9].

Between 16 and 26 weeks of pregnancy, there is a high risks to develop fetal cardiac injuries, manifested as congenital autoimmune heart block, endocardial fibroelastosis and myocarditis, which can progress to dilated cardiomyopathy[30-32].

The reported prevalence of congenital atrioventricular heart block *in utero*, at birth or in the neonatal period is 1-2%[4]. Irreversible third-degree cardiac heart block is the most serious manifestation of congenital neonatal lupus, requiring a cardiopediatric specialist and management with cardiac pacemaker implantation. Congenital neonatal lupus is associated with higher rates of intrauterine and perinatal mortality and morbidity.

The effects of rheumatological pathology on the pregnant women are: hypertension, antepartum hemorrhage, severe maternal morbidity (cardiac arrest, shock, respiratory failure, cerebrovascular hemorrhage)[33].

Plasmapheresis, immunoglobulins or beta-sympathomimetics have also been cited in the literature as alternative therapies, but without having a clear indication

of improving the evolution of pregnant women with Sjögren syndrome[22].

An increased rate of preterm deliveries was found in most studies. As a consequnce, birth weight was significantly lower in newborns from mothers with Sjögren's syndrome (3010 g) compared to the control group (3458 g)[38]. De Carolis proposed placental insufficiency as a mechanism for low birth weight (LBW) due to immune imbalance[40]. The presence of anticardiolipin and antiphospholipids can lead to placental vasculitis, placental insufficiency, thrombosis or infarction[41].

When considering the relationship between placental growth and immune imbalance, only the link between hCG secretion and aPL antibodies has been demonstrated. Schwartz et al. showed in their study how aPL antibodies reduce placental and indirectly hCG development. Such a link was not found between anti-Ro, anti-La and hCG antibodies, thus suggesting that they do not influence placental growth[42].

In addition, the risk of fetal loss associated with Sjögren's syndrome can be questioned, given that many studies in the literature are from the 1990s. Recently, we have seen that the associated risks decrease in incidence, and in many studies there is no statistically significant difference compared to the control group. Carolis et al. have also raised the issue of woman's age at the time of conception. Women with Sjögren's syndrome often show a systematic, severe symptomatology in their youth that causes them to postpone conception for a long period of time, until the symptoms subside. This fact makes pregnant women much older, which in turn comes with risks of fetal loss, spontaneous abortion, stillbirth, genetic abnormalities and preterm deliveries. These overlap with the complications of the association between Sjögren's syndrome and pregnancy. Given the above, it becomes difficult to find the exact cause of the development of the complication[40].

Microhymerism

Nowadays, the phenomenon of coexistence of two populations of cells originating from different individuals, present in a single person, is being studied. The transfer of fetal cells into the mother's blood is already well known, but their persistence has also been demonstrated[43]. There is also the problem of histocompatibility of the fetal semi-allogenic cells, which can lead to an immune reaction. Fetal cells will differentiate into host tissues, thus participating in tissue injury responses. This process of microhymerism has also been shown in Sjögren's syndrome[44]. Using the FISH technique, a significant difference was found between the detection of male cells in the labial salivary glands compared to the control group (55% versus 12%)[45]. In another study, coordinated by Aractingi, a frequency of 45% was noted in the detection of male cells in women's blood, but only in the context of secondary Sjögren's syndrome[46].

Thus, the etiology of Sjögren's syndrome determined by the passage of fetal cells into the maternal blood and by the immune response triggered by them becomes evident.

Postpartum management

Case tracking does not end at birth. This must continue for both the mother and the newborn. The complications and repercussions of autoimmune pathology on the fetus should be treated, but the maternal exacerbations should also be followed, as their presence in the postpartum period is well known.

Table 1 Pregnancy complications founded in association with Sjögren syndrome

Study	Number of pregnancies	Pregnancy complications
Siamopoulou Mavridou et al., 1995(34)	63	Premature delivery, spontaneous abortions, stillbirth, fetal loss
Takaya et al., 1991(35)	39	Spontaneous abortions, premature delivery, artificial abortion, stillbirth
Skopouli et al., 1994(36)	207	Spontaneous abortions, stillbirth, premature delivery, induced abortion, total fetal loss
Julkunen et al., 1995(37)	55	Fetal loss, spontaneous abortions, premature delivery, intrauterine growth restriction, stillbirth
Hussein et al., 2011(38)	80	Miscarriage, premature delivery, low birth weight, small for gestational age, fetal death, congenital heart block
Priori et al., 2013(39)	45	Miscarriage, fetal death, neonatal death, induced abortion, preterm delivery, congenital heart block
De Carolis et al., 2014(40)	34	Spontaneous abortions, stillbirth, preterm delivery, fetal loss, intrauterine growth restriction, low birth weight, induced abortion

Conclusions

Pregnant women with Sjögren's syndrome should be closely monitored throughout their pregnancy, both for tracking the evolution of the autoimmune pathology and for the possible fetal complications that may arise. Serial fetal cardiac ultrasounds and maternal antibody titration are required, as well as standard assessments of pregnancy progression. All newborns, even asymptomatic, should be followed-up in order to eliminate the progressive lesions due to intrinsic factors. Most studies are done for secondary Sjögren's syndrome and they have showed an increased risk of: spontaneous abortion, stillbirth, neonatal deaths, intrauterine growth restriction, premature birth, oligohydramnios, adrenal suppression, small for gestational age, but also hypertension, antepartum hemorrhage and severe maternal morbidity (cardiac arrest, shock, respiratory failure, cerebrovascular hemorrhage) for the pregnant woman.

The treatment with hydroxychloroquine, dexamethasone or betamethasone has scientifically proven beneficial effects only in the cases of incomplete congenital heart block or in recently established congenital heart block.

The phenomenon of microhymerism, which can occur after a pregnancy, is also interesting to watch. The coexistence of the two cell types can be the trigger for the onset of an autoimmune pathology such as Sjögren's syndrome. This process is still under study, but its presence in Sjögren's syndrome has already been highlighted. ■

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