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Review

The impact of primary Sjogren's syndrome on pregnancy outcome: Our series and review of the literature

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ABSTRACT

Objective: Firstly, to investigate the pregnancy outcome of women with primary Sjogren's Syndrome (pSS) in a case–control study; secondly, to perform a review of the literature in order to clarify if the pregnancy outcome is affected by pSS and influenced by the disease clinical onset.
Method of study: Thirty-four pregnancies with pSS and 136 controls were retrospectively collected.
Results: Six pregnancies occurred before the pSS diagnosis and 28 after the pSS diagnosis. Two cases were complicated by intrauterine atrio-ventricular block. A statistically significant increase of the rate of spontaneous abortions, preterm deliveries and cesarean section was found in pSS pregnancies. The mean neonatal birth weight and the mean neonatal birth weight percentile were significantly lower in the offspring of women with pSS in comparison to controls. Similar pregnancy outcome was observed in women with pSS diagnosis before and after the index pregnancy.
Conclusions: Women with pSS experienced complicated pregnancies more frequently than controls, regardless of the onset of the symptoms, showing that the immunological disturbance is present throughout the reproductive life.

Contents

1. Introduction

Sjogren's syndrome is a chronic autoimmune inflammatory disease that can present either alone, primary Sjogren's syndrome (pSS), or in the context of an underlying connective tissue disease, most commonly rheumatoid arthritis, or systemic lupus erythematosus (secondary Sjogren's syndrome) [1]. It is one of the most common autoimmune diseases with a 0.1–4.8% prevalence rate in the total female population; it may occur at any age, but it affects mainly women at the fourth decade of life; the female:male ratio is estimated equal to 9:1 [2]. These data and the first pregnancy advanced age of the last years explain the increased frequency rate of pregnancies in women with pSS.

The hallmark of fetal outcome in SS is the congenital heart block (CHB). It is the most severe complication that may affect the offspring of women with SS and it is attributed to anti-Ro/SSA and/or anti-La/SSB-mediated damage of the atrio-ventricular node. The occurrence rate of CHB has been estimated at approximately 2% in all infants born to women with anti-Ro/SSA antibodies [3–7] and 3% in all infants born to women with anti-La/SSB [8–10]. The recurrence rate in a mother

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with antibodies, who has a previous child affected, is approximately 16–18% [3,8,11]: it is nearly nine times higher than the risk for CHB in a primigravida with the candidate antibodies. About the sex ratio of CHB, the feminine predisposition for CHB is not clearly established. According to the studies, the proportion of girls among children having CHB is variable from 83% [12] to 50% [13] in a larger sample. Autoantibody-associated CHB carries a substantial morbidity and mortality. The majority of surviving affected children requires permanent pacing before adulthood [10]: 33–53% [7,13] require subepicardial pacemaker in the neonatal period; in the late ages, this percentile raised to 60% [10,13]. The CHB mortality is variable from 12% to 43% in literature [8,13–16] and it increases when the disease is associated with endocardial fibroelastosis or cardiomyopathy [17]. When CHB is diagnosed, an intrauterine therapy is possible to increase the atrioventricular conduction speed and improve the fetal outcome. Maternal treatment with fluorinated steroids, as dexamethasone or betamethasone, can reduce the antibody-mediated inflammatory damage of nodal tissue. The alternatives/additional therapies include the plasmapheresis, intravenous immunoglobulins and betasympathomimetics [18].

However, excluding the reports on CHB, the study results on pregnancy outcome of women with pSS are few and conflicting. Two series have reported increased rate of spontaneous abortions and fetal losses [19,20] not related to anti-SSA, anti-SSB, or antiphospholipid antibodies. Other studies did not confirm these data, but underlined that pregnant women with pSS had more advanced age, with offspring having a high rate of SGA and lower mean birth weight. Furthermore, less frequency of normal partus was observed [21].

For other autoimmune diseases, the impact on pregnancy outcome is well established and it differs according to the maternal disease, disease activity, severity of organ damage, antibody profile and drug treatment [22]. Among autoimmune diseases, systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS) have been widely studied for their detrimental effects on fetal and maternal health, showing a higher risk of fetal losses, premature deliveries, preeclampsia, and IUGR [22–28]. It is also noteworthy that some obstetrical complications may precede the clinical onset of connective tissue diseases [29] or indicate the presence of underlying autoimmune diseases [30].

These issues have not been carefully addressed in pSS, prompting us to perform a review of the literature on pregnancy outcome in women with pSS, including our case–control study. In order to clarify if the pregnancy outcome was affected by the disease clinical onset, in our series, data of pregnancy before and after pSS diagnosis were analyzed according to the timing of pSS diagnosis.

2. Materials and methods

Thirty-four pregnancies in 22 women with pSS, followed at our tertiary referral center between 2002 and 2012, were retrospectively collected. All the included patients fulfilled the American European Consensus Criteria (AECC) for pSS [31].

In addition, one hundred and thirty six healthy pregnancies were evaluated as controls. Data about pregnancy outcome in both groups were obtained from electronic case records of our center. In particular, the number of spontaneous abortions ($\leq$20 weeks of gestation), stillbirths (the intrauterine death > 21th week of gestation and before birth), fetal losses (the sum of spontaneous abortions and stillbirths), preterm deliveries (<37 + 0 week of gestation), low birth weight neonates (LBW: defined as birth weight < 2500 g) and IUGR (defined as a birth weight percentile < 10th according to a national standard curve) [32] were analyzed as indicators of obstetric outcome. The following informations were also extracted from the delivery register and evaluated in the two groups: way of delivery, gestational week at delivery, neonatal birth weight, and neonatal birth weight percentile.

The serum immunological profile of women affected by pSS during pregnancy was also analyzed. Patients were profiled for the following antibodies: anti-nuclear antibodies (ANA, detected by immunofluorescence analysis; ANA titer is positive when it is $\geq$1:80) and anti-Ro (SSA) and La (SSB) cellular antigen antibodies (detected by ELISA; their titles were positive in case of $\geq$25 UI/ml). In addition the presence of rheumatoid factor (RF), anti-double stranded DNA IgG antibodies (anti-dsDNA, detected by ammonium sulfate precipitation according Farr), anti-cardiolipin IgG and IgM antibodies (aCL, detected by ELISA), anti-beta2 glycoprotein I IgG and IgM antibodies (antiβ2GPI, detected by ELISA) and Lupus anticoagulant (LA, determined by activated partial-thromboplastin time, aPTT-, aT diluted with phospholipids, Kaolin time and tissue thromboplastin inhibition test) were assessed.

Normally distributed continuous variables were compared using a two-sample Student *t* test. Cross tabulation and Chi-square (with Yates' continuity correction) were used to examine the relationship between nominal variables. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Demographic data

Maternal age at delivery was significantly higher in women with pSS (mean = 34.8 years) vs controls (30.2 years; $P = 0.0005$).

Among the 34 pregnancies, in the 22 women with pSS, six pregnancies (18%) occurred before the pSS diagnosis and 28 (82%) after the pSS diagnosis. In the 6 pregnancies that occurred before the pSS diagnosis, the time between the index pregnancy and the disease diagnosis was 6.6 years; whereas, in the 28 pregnancies that occurred after the pSS diagnosis, the mean disease duration was 4.1 years.

As regards the women with pSS diagnosis before pregnancy, no case of systemic disease was observed during pregnancy; no patient was also receiving cytotoxic drugs during or before pregnancy. According to their disease clinical state, these women received specific medical treatment during pregnancy, consisting of steroids in 12 cases (43%), and antimalarian drugs in 13 cases (46%) with or without steroids. Low-dose aspirin was administered in 13 cases (46%).

In the 28 pregnancies that occurred after the pSS diagnosis, the incidence of ANA and Ro/SSA positivity was 82% and 100%, respectively. Anti-La/SSB and RF were positive in 61% and 36%, respectively. Finally, 39% of the pSS patients had one or more antiphosholipid antibody (aPL) positivity, but no case fulfilled the revised classification criteria of APS [26].

3.2. Pregnancy outcome

Among the 34 pregnancies in women with pSS, 10 pregnancies (29%) ended in spontaneous abortions, and no case of stillbirth was registered. One voluntary abortion (3%) was observed in a case complicated by fetal diagnosis of Klinefelter syndrome. So, the live birth rate consisted of 68%.

The results of pregnancy outcome in 34 patients with pSS compared to that in 136 controls are shown in Table 1. The obstetrical outcome in terms of mean week at delivery, mean neonatal birth weight and mean neonatal birth weight percentile was encountered in pSS patients in comparison to that of controls, as shown in Table 1.

Two pregnancies (9%) were complicated by CHB: they occurred after the pSS diagnosis. In the first case with CHB, a Chickenpox infection complicated the pregnancy in the first trimester, requiring the reduction of the ongoing steroid treatment. By serial fetal echocardiographic evaluation, a third degree intrauterine AV block was identified at 24 gestational weeks, so the treatment with high-dose betamethasone was started. A preterm delivery (31th gestational week) was needed because of fetal distress, with a live female infant weighting 1210 g (Apgar score 7^1, 8^5). The neonate required a pace-maker implantation within the first 12 h of life; at 5 years follow up, she is in good health. In the second case, the CHB was diagnosed at 22 gestational weeks; then, high-dose betamethasone was administered. This pregnancy ended with a delivery at the 32nd gestational week of a live female