Risk factors for Sjögren's syndrome: a case-control study

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Abstract

Objective

The aim of this study was to investigate potential risk factors for Sjögren's syndrome (SS) by means of a multi-centre case-control study, focusing in particular on familial and environmental risk factors. 140 female SS patients and 109 female controls with orthopaedic problems were consecutively enrolled in seven university hospitals in Italy.

Methods

Information regarding the patient's lifestyle, her medical, menstrual and pregnancy history, and any family history of autoimmune diseases (AD) was obtained through a detailed structured questionnaire. The odds ratio (OR) and 95% confidence interval (95%CI) were calculated using unconditional logistic regression, adjusting for age and family size. The probability of first-degree relatives developing an autoimmune disease was also investigated.

Results

A positive family history of AD was significantly associated with SS. Subjects with a first-degree relative (FDR) with AD showed a seven-fold increase in the risk for SS compared to controls (OR=7.4, 95%CI 2.8 – 20.1); the strength of this association increased with the number of relatives affected. Similarly, the FDR of SS patients had a higher risk of AD in comparison to subjects without FDR affected by SS. Women with one or more pregnancies had an increased risk of SS (OR=2.1, 95%CI 1.0 – 4.3).

Conclusion

This study suggests that a family history of AD is associated with SS.

Key words

Sjögren's syndrome, smoking, pregnancy, transfusions, familial aggregation, risk factors.

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Introduction

Sjögren's syndrome (SS) is a chronic autoimmune disease mainly characterized by sicca syndrome (dry eyes and dry mouth). However, other organs may be involved and the disease is now considered to be systemic. The ethiopathogenesis of SS is still not known; genetic as well as infectious factors have been suggested. For other autoimmune diseases (AD), some epidemiologic studies have focused on a family history of autoimmune diseases, smoking, silicone breast implants, estrogens, and hair dye, with conflicting results for different disease conditions (1). As far as we know, no case-control study has been conducted on SS patients regarding the role of potential risk factors, except for one study that focused on perinatal factors (2).

The main purpose of our study was to evaluate the association between SS and specific factors such as consanguinity between parents, reproductive history, age at menarche and menopause, blood transfusions, smoking and a family history of AD in first-degree relatives (FDR). We also investigated the probability of first-degree relatives of SS patients developing an autoimmune disease.

Materials and methods

A multi-centre case-control study was performed in seven outpatient clinics of rheumatology and internal medicine in Italy. Patients with primary SS, systemic lupus erythematosus (SLE) and controls were recruited at the same time. Subsequently, the SLE and SS cases were analyzed separately using the same controls as the comparison group. The results for the SLE cohort have been published recently (3). Primary SS cases were identified according to the Euro-American SS classification criteria (4) and consecutively enrolled during follow-up visits. It has been reported that 33.3% of patients with primary SS develop an additional autoimmune disease (5). Since recently there has been some debate regarding the classification of SS in the presence of another autoimmune disorder, and the term "secondary SS" is widely used when SS represents just one feature in the spectrum of another connective tissue disease (CTD) such as RA (6, 7), in this work we use the term "associated SS" to define a patient who satisfies the Euro-American SS classification criteria for primary SS and one or more overlapping AD, not necessarily a CTD.

Controls were in-patients with no history of AD, who had been hospitalized in the same period in orthopaedic departments in the same catchment areas, none of whom were taking opioids or painkillers.

A trained interviewer in each clinic collected the data for this study using a detailed, 45-minute questionnaire designed to obtain information on the patient's demographic characteristics, medical history, and other possible risk factors, such as a family history of AD, consanguinity between parents, smoking habits, blood transfusions, and reproductive and menstrual history (age at menarche and menopause). With regard to the family history of AD, data were collected on the vital status and age of all FDR (parents, siblings, children), and the age at death and/or age at diagnosis of AD, if applicable. In responding to the questions on the family history of AD, participants were shown a list of 31 ADs, including those for which there is direct or indirect evidence of an autoimmune pathogenesis (8). The consistency of the family history was verified as previously described (3). The collected samples were analyzed not only in accordance with a classical case-control study, but also as a retrospective follow-up study in order to estimate the incidence and risk of AD among the FDR of SS patients. In particular, we estimated the Incidence Density rates and their confidence intervals (95%) for AD among the group of FDR of the cases and controls. For each relative the person years (py) at risk were estimated as the total number of years before the diagnosis of AD or death or the interview. The risk of developing an autoimmune disease among the FDR of SS patients compared with the relatives of controls was estimated, taking into account the non-independence of family members (9).

Regarding smoking habits, cases and

controls were classified into three groups: (i) regular smokers, defined as subjects smoking at least one cigarette per day for at least 3 months; (ii) ex-smokers if they had stopped smoking for at least one year before the diagnosis for the patients, and before the interview for controls; and (iii) non-smokers. Smokers were also asked to specify their age when they started smoking, and the dates of giving-up and re-starting where applicable. As in similar retrospective studies (10, 11), analysis was restricted to the patient's smoking history before the SS diagnosis. Strong evidence exists that subjective recalled smoking data are accurate and reliable (12). All events such as blood transfusions, pregnancy and age at menarche and menopause that occurred after the diagnosis of SS were excluded from the analysis. Participants were also asked to indicate the number of pregnancies and abortions (either spontaneous or induced) and their age at the time of the event. Moreover, in order to evaluate the role of pregnancy as a risk factor, we stratified the cases into those with isolated SS and those with associated SS where, as specified above, associated cases were probands with other concomitant ADs.

The data collected were analysed using STATA software. The hypothesis of an association between the different risk factors and SS was investigated by producing tables with the percentage distributions of each variable among the cases and controls, and estimating the age-adjusted odds ratios (OR) and their confidence intervals (95%CI). To estimate the confidence intervals, we used the Woolf method, except when OR equaled infinity (based on a zero cell), for which we set the upper confidence limit to infinity and determined the lower limit using the Cornfield method. Finally, to take into account the possibility of any confounding factors, the most relevant variables were selected and their effects were adjusted using logistic regression models.

Results

Two hundred and eighty-three subjects were enrolled: 143 patients with SS and 140 controls. As only 3 men were included among the cases, the analysis was restricted to women (140 cases and 109 controls). Table I shows selected socio-demographic characteristics of the cases compared to the controls.

Table I. Socio-demographic characteristics by Sjögren's syndrome cases and controls.

	Cases (n = 140)		Controls (n = 109)	
	N	%	N	%
Age at interview (years)				
≤ 34	16	11.4	30	27.5
35-44	24	17.1	23	21.1
45-54	24	17.1	18	16.5
55-64	45	32.1	17	15.6
≥ 65	31	22.1	21	19.3
Marital status				
Single	12	8.6	26	23.8
Married	112	80.0	67	61.5
Separated/divorced	3	2.1	7	6.4
Widow	13	9.3	9	8.3
Education				
Primary school	50	35.7	26	24.1
Middle school	38	27.1	22	20.4
High school	37	26.4	38	35.2
College	15	10.7	22	20.4

Table II. Distributions of the different risk factors among cases and controls and age-adjusted OR.

Risk factors	Cases (n = 140)		Controls (n = 109)		OR (95%CI)
	N	%	N	%	
Consanguinity					
No	137	97.9	107	98.2	1
Yes	3	2.1	2	1.8	1.3 (0.2–8.3)
Smoking habits					
Non smokers	94	67.6	70	64.8	1
Smokers	21	15.1	25	23.2	0.8 (0.4–1.6)
Ex-smokers	24	17.3	13	12.0	1.5 (0.7–3.1)
Blood transfusion					
No	114	87.7	86	81.1	1
Yes	16	12.3	20	18.9	0.6 (0.3–1.2)

Among the SS patients, 101 had the isolated form of the disease and 39 (27.9%) had at least one associated AD such as autoimmune thyroid disease (ATD) (16 cases with Hashimoto thyroiditis and 3 with Basedow disease), rheumatoid arthritis (RA) (5 cases), psoriasis (4 cases), systemic sclerosis (3 cases), systemic vasculitis (3 cases), insulin-dependant diabetes (2 cases), vitiligo (2 cases) or SLE, myasthenia gravis, idiopathic thrombocytopenic purpura, autoimmune hepatitis, celiac disease, or inflammatory bowel disease (one case each). These 39 patients all satisfied the Euro-American SS classification criteria for primary SS, and therefore represented cases of true overlap syndromes rather than secondary SS and in fact the percentage of primary SS patients with at least one associated AD in this cohort was similar that previously reported (5).

Tables II and III show the frequency distribution among cases and controls of the risk factors studied, and their age-adjusted OR.

Table II shows that the patients were less disposed to smoke than the controls (15.1% *vs* 23.2%) and there were more ex-smokers among SS patients than among the controls (17.3% *vs* 12%). The age-adjusted OR for smokers was 0.80 (95%CI 0.40 – 1.60).

No association was found between the risk of developing SS and previous blood transfusions (OR = 0.58, 95%CI

Table III. Frequency distributions of reproductive history among cases and controls and age-adjusted OR.

	Cases (n = 140)		Controls (n = 109)		OR (95%CI)
	N	%	N	%	
Reproductive history					
Births					
0	22	17.3	39	35.8	1
≥ 1	105	82.7	70	64.2	2.5 (1.3–4.7)
Spontaneous abortion					
0	112	82.9	89	83.2	1
≥ 1	23	17.0	18	16.8	0.9 (0.5–1.9)
Voluntary abortion					
0	123	91.1	100	93.5	1
≥ 1	12	8.9	7	6.5	1.4 (0.5–3.8)
Still births					
0	136	98.5	107	100	
≥ 1	2	1.5	0		-
Total pregnancy					
0	25	18.7	36	33.6	1
≥ 1	109	81.3	71	66.4	2.2 (1.1–4.2)
Menstrual history					
Age at menarche (years)					
8-14	127	90.7	98	90.7	1
≥ 15	13	9.3	10	9.3	1.0 (0.4–2.4)
Age at menopause (years)					
29–47	31	36.5	15	34.9	1.4 (0.5–3.5)
48–51	20	23.5	13	30.2	1
≥ 52	34	40.0	15	34.9	1.5 (0.6–3.7)

Table IV. Crude (ORc) and adjusted (ORa) odds ratios in the association of Sjögren's syndrome with autoimmune disease in first degree relatives.

	Cases		Controls		ORc (95%CI)	ORa (95%CI)[A]
	N	%	N	%		
FDR affected by AD						
No	107	76.4	104	95.4	1	1
Yes	33	23.6	5	4.6	6.4 (2.3–17.7)	7.4 (2.8–20.1)
Number of Relatives affected						
0	107	76.4	104	95.4	1	1
1	26	18.6	5	4.6	5.1 (1.9–13.7)	5.6 (2.0–15.4)
≥ 2	7	5.0	0	–	∞ (1.74 - ∞)[§]	nc*

[A] ORa, odds ratio adjusted for probands age and family size.
*Not calculated because of the 0 cell.
[§] See text for method of computation.

0.28–1.20) or consanguinity between parents (OR = 1.32, 95%CI 0.21–8.32). The relationships between the patients' menstrual and obstetric history and Sjögren's syndrome are shown in Table III. There was no association between the risk of developing SS and the age at menarche or menopause, even if more women in the SS group had a late menopause than the control group (40% *vs* 34.9%). With regard to the obstetric history, significant differences were observed in the frequency distribution of births (82.7% *vs* 64.2%, OR = 2.5) between the cases and controls. Overall, compared to nulliparous women, parous women (at least one pregnancy) had a higher risk of developing SS (age-adjusted OR = 2.2; 95%CI 1.1– 4.2).

With regard to familial aggregation, a significant difference in the number of SS probands with at least one first-degree relative with an AD compared to controls was found: 33 out of 140 (23.6%) *vs* 5 out of 109 (4.6%), respectively. After adjusting for the probands' age and family size, a history of ADs in FDR was found to have a statistically significant effect on the risk of SS (OR = 7.4, 95%CI 2.8 – 20.1, Table IV). ATD was the most prevalent autoimmune disease among the FDR of SS patients (6 out of the 43 ADs found) followed by undifferentiated connective tissue disease (5/43), RA (4/43), SLE (4/43), insulin-dependant diabetes (4/43), psoriasis (4/43), seronegative polyarthritis (3/43), autoimmune thrombocytopenia (2/43), anti-phospholipid antibody syndrome (2/43) and systemic vasculitis (2/43). Other ADs were found in single cases; only one FDR had SS. None of the controls' first-degree relatives had more than one AD, the most frequent being psoriasis (2/5), followed by RA, ulcerative colitis and ATD (one case each). None of the controls enrolled in the study had more than one FDR with AD, while seven SS cases had two or more affected relatives.

No differences between sporadic and familial cases were found when we considered features such as marital status, smoking habits, education and reproductive history. On the contrary, differences between the two groups for age at the interview (51.1 *vs* 43.7 years) were observed. For this reason, all the OR shown were adjusted for the age of the probands. Patients with a family history of AD had a low mean age at diagnosis compared to patients without such a family history. The relationship between the probands and their relatives, the mean age, and the percentage of affected FDR are shown in Table V.

There was no significant difference between the mean number of FDR among the cases and controls (5.9 *vs* 5.8) and the percentage of female FDR was similar in the cases and controls. When the FDR were divided by sex, more ADs were found among the sisters and daughters of cases and similarly, although in a smaller number, among the FDR of controls (data not shown).

Table VI reports the odds ratios for SS

Table V. Characteristics of first degree relatives of probands.

	Cases families				Controls families			
	N	Mean age	N With AD	% With AD	N	Mean age	N With AD	% With AD
First degree relatives	*824*	*51.6*	*43*	*5.2*	*634*	*50.3*	*5*	*0.8*
Mother	129	71.0	8	6.2	109	66.6	0	0.0
Father	134	68.7	6	4.5	107	65.7	1	0.9
Sisters	172	52.8	12	7.0	149	51.0	2	1.3
Brothers	180	51.7	5	2.8	136	46.8	1	0.7
Daughters	94	30.2	8	8.5	61	28.1	1	1.6
Son	115	25.6	4	3.5	72	26.6	0	-

Table VI. Results of unconditional logistic regression analysis overall and by isolated and associated Sjögren's syndrome (OR adjusted for age and family size).

	All Cases		Isolated Sjögren's syndrome		Associated Sjögren's syndrome	
	OR	95%CI	OR	95%CI	OR	95%CI
History of AD in FDR	5.2	2.0–13.5	4.7	1.8–12.4	7.5	2.6–21.8
Previous pregnancy	2.1	1.0–4.3	1.6	0.8–3.5	5.8	1.5–22.9
Smoking habits						
Smokers	0.7	0.3–1.4	0.5	0.2–1.1	1.5	0.5–4.4
Ex-smokers	1.5	0.7–3.2	1.2	0.5–2.8	2.5	0.9–7.0

Table VII. Risk for developing autoimmune diseases among first degree relatives of cases and controls.

First degree relatives	Cases	Controls
Affected by AD	43	5
Incidence Density rate of AD	1.02x1000 (95% CI 0.76-1.38)	0.16x1000 (95% CI 0.06-0.38)
OR* of AD	7.04 (95% CI 2.76-17.99)	1

*OR adjusted for age and sex of relatives.

estimated by logistic regression; specifically we evaluated the risk of developing SS overall and based on the presence/absence of other ADs.

The results of multivariate analysis confirmed that adjusting for potential confounders, a history of ADs in FDR and previous pregnancy are still important risk factors. When we compared patients with SS alone and patients with SS associated with other ADs, the effect of pregnancy was significantly different in the two groups. In particular, we found that among women with other ADs and a history of pregnancy, the risk of developing SS (OR = 5.8, 95%CI 1.5–22.9) increased significantly (test of heterogeneity of ORs: $\chi 2 = 1.77$, $p = 0.18$) compared to women without an additional AD (OR = 1.6, 95%CI 0.8–3.5). A family history of AD was associated with both the isolated and the associated forms of SS.

As show in Table V, a significantly higher percentage of first-degree relatives of SS patients were affected with autoimmune diseases (5.2%) than the FDR of controls (0.8%). In order to take into account the family size and the age of the FDRs in the analysis, we estimated the Density Incidence rate of any AD in the FDR of the cases and controls. Among the 1,458 first-degree relatives of the cases and controls, a significant difference was found in the rate of ADs between the cases (1.02 x 1000 py) and controls (0.16 x 1000 py).

The results of the unconditional logistic regression model with adjustment for correlated data are presented in Table VII. The risk (OR) of having an AD among the FDR of SS patients compared with the relatives of controls was 7.04 (95%CI 2.76 –17.99)

Discussion

Several reports have previously described a familial aggregation of ADs in SS (13-17). To the best of our knowledge, this is the first epidemiologic study demonstrating that the prevalence of ADs is raised in the first-degree relatives of SS patients. Moreover, our results suggest that a family history of AD is significantly associated with SS and that the strength of this association increases with the number of affected relatives. These results confirm the importance of genetic factors in the pathogenesis of SS and suggest that clinically different autoimmune phenotypes may share the same susceptibility genes, such as HLA-DR3, which could act as predisposing risk factors for autoimmune disorders. Other specific genes that may play a contributing role remain to be discovered. No differences in marital status, smoking habits, education or reproductive history were found between patients with, compared to patients without, a family history of AD. It is worth noting that the former group was characterized by a low mean age at diagnosis, probably as a consequence of an early diagnosis or early onset of the disease.

Cigarette smoking has been associated with an increased risk of developing SLE (11, 18) and RA (10). In this study, a mild negative association between smoking status and SS was observed. The lower number of smokers among SS patients could be a result of oral discomfort already present before the SS diagnosis, leading to changes in smoking habits. However, the possibility of a protective effect of smoking should not be dismissed as it is well known that some immune-mediated chronic inflammatory diseases, such as ulcerative colitis and Behçet's disease, are less frequent among smokers and may flare up after a patient has quit smoking (19, 20). On the other hand, it is also possible that the current criteria for SS,

which were used in this study, could be appropriate for the classification of SS among non-smokers, but may miss a proportion of SS patients among smokers. Manthorpe *et al*. (21) demonstrated that smoking reduces the focus score in the minor salivary glands by reducing the concentration of lymphocytes/plasma cells and hence the production of the diagnostic autoantibodies. Therefore, smoking could invalidate the classification criteria for SS, which relies principally on histological findings and the presence of anti-Ro and anti-La antibodies. This point is still the subject of debate.

As far as we know, no other studies have investigated the effect of previous pregnancies on the risk of developing SS. Our finding of an increased risk of SS in women with previous pregnancies suggests that immunobiologic modifications during pregnancy could be involved in the pathogenesis of SS. Several studies support a role of prolactin (PRL) in the pathogenesis of SS (22-24). An interesting hypothesis has suggested that raised prolactin levels may be responsible for the increased rates at which cells secrete autoantigens to the surrounding tissue space and expose epitopes that previously were cryptic (25, 26). A further possible explanation for the link between pregnancy and the increased risk of developing SS is microchimerism. During pregnancy foetal cells can be transferred to the mother, and these may persist for decades. This naturally acquired microchimerism has been proposed as a possible target for the autoimmune response in different ADs (27), although its role in SS is still controversial (28-30). Cells from one individual can also be acquired iatrogenically by another following a transplant or blood transfusion (27). In the present study no association was found between blood transfusions in the patient before the SS diagnosis and the SS itself.

Our initial analysis showed that pregnancy represents a risk factor for SS patients, but when we grouped the patients into those with SS alone and those with SS in association with another AD we found that the effect of the history of a previous pregnancy on the development of SS differed. Pregnancy and other ADs seem to act synergistically in increasing the risk of SS. After analysing the chronologic relationship of the events, it is possible to hypothesize that a pre-existent AD (which suggests a genetic background predisposing to autoimmunity) and a previous pregnancy (with its associated immunobiologic modifications) enhance the risk of SS.

In conclusion, the familial aggregation of SS with other ADs has been confirmed in this study. The first-degree relatives of patients with SS are seven times more likely to have an AD in comparison to the FDR of controls. Vice versa, a family history of autoimmune disorders is clearly associated with SS. We have also shown that pregnancies are associated with an increased risk of developing SS. A negative, although not significant, association between smoking and SS was found but this observation requires further investigation.

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References

1. DOOLEY MA, HOGAN SL: Environmental epidemiology and risk factors for autoimmune diseases. *Curr Opin Rheumatol* 2003; 15: 99-103.
2. MOSTAFAVI B, AKYUZ S, JACOBSSON ME, NILSEN LV, THEANDER E, JACOBSSON LH: Perinatal characteristics and risk of developing primary Sjögren's syndrome: a case-control study. *J Rheumatol* 2005; 32: 665-8.
3. PRIORI R, MEDDA E, CONTI F *et al*.: Familial autoimmunity as a risk factor for systemic lupus erythematosus and vice-versa: a case-control study. *Lupus* 2003; 12: 735-40.
4. VITALI C, BOMBARDIERI S, JONSSON R *et al*.: European study group on classification criteria for Sjögren's syndrome. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus group. *Ann Rheum Dis* 2002; 61: 554-8.
5. LAZARUS MN, ISENBERG DA: Development of additional autoimmune diseases in a population of patients with primary Sjögren's syndrome. *Ann Rheum Dis* 2005; 64: 1062-4.
6. ISENBERG DA: Systemic lupus erythematosus and Sjögren's syndrome: Historical perspective and ongoing concerns: *Arthritis Rheum* 2004; 50: 681-3.
7. MANOUSSAKIS MN, GEORGOPOULOU C, ZINTARAS E *et al*.: Sjögren's syndrome associated with systemic lupus erythematosus: clinical and laboratory profiles and comparison with primary Sjögren's syndrome. *Arthritis Rheum* 2004; 5: 882-91.
8. ROSE NR, BONA C: Defining criteria for autoimmune diseases. *Immunology Today* 1993; 14: 425-30.
9. LIANG KY, ZEGER SL, QAQISH BF: Multivariate regression analyses for categorical data. *J Royal Stat Soc* 1992; 54: 3-40.
10. SILMAN AJ, NEWMAN J, MACGREGOR AJ: Cigarette smoking increases the risk of rheumatoid arthritis: results from a nationwide study of disease discordant twins. *Arthritis Rheum* 1996; 39: 732-5.
11. HARDY CJ, PALMER BP, MUIR KR *et al*.: Smoking history, alcohol consumption and systemic lupus erythematosus: a case-control study. *Ann Rheum Dis* 1998; 57: 451-5.
12 PIERCE JP, DWYER T, DI GIUSTO E *et al*.: Cotinine validation of self-reported smoking in commercially run community surveys. *J Chronic Dis* 1987; 40: 689-95.
13. MOLTA CT, KHAN MA, APONTE CJ *et al*.: Familial occurrence of systemic sclerosis, rheumatoid arthritis and other immunological disorders: reports of two kindreds with study of HLA antigens and review of the literature. *Clin Exp Rheumatol* 1989; 7: 229-36.
14. COLL J, RIVES A, GRINO MC *et al*.: Prevalence of Sjögren's syndrome in autoimmune diseases. Ann Rheum Dis 1987; 46: 286-9.
15. FOSTER H, FAY A, KELLY C *et al*.: Thyroid disease and other autoimmune phenomena in a family study of primary Sjögren's syndrome. *Br J Rheumatol* 1993; 32; 36-40.
16. BOLING EP, WEN J, REVEILLE JD *et al*.: Primary Sjögren's syndrome and autoimmune hemolytic anaemia in sisters. *Am J Med*. 1983; 74: 1066-71.
17. TANAKA A, IGARASHI M, KAKINUMA M *et al*.: The occurrence of various collagen diseases in one family: a sister with ISSc, PBC, APS, and SS and a brother with systemic lupus erythematosus. *J Dermatol* 2001; 28: 547-53.
18. GHAUSSY NO, SIBBIT WLJ, QUALLS CR: Cigarette smoking, alcohol consumption and the risk of systemic lupus erythematosus: a case control study. *J Rheumatol* 2001; 28: 2449-53.
19. SOY E, ERKEN E, KONCA K, ORBEK S: Smoking and Behçet's disease. *Clin Rheumatol* 2000; 19: 508-9.
20. BIRRENBACH T, BOCKER U: Inflammatory bowel diseases and smoking: a review of epidemiology, pathophysiology and therapeutical implications. *Inflamm Bowel Dis* 2004; 10: 848-59.
21. MANTHORPE R, BENONI C, JACOBSSON L *et al*.: Lower frequency of focal lip sialadenitis in smoking patients. Can tobacco diminish the salivary gland involvement as judged by histological examination and anti-SSA/Ro and anti-SSB/La antibodies in SS? *Ann Rheum Dis* 2000; 59: 54-60.
22. HAGA HJ, RYGH T: The prevalence of hyperprolactinemia in patients with primary Sjögren's syndrome. *J Rheumatol* 1999; 26: 1291-5.
23. DING C, CHANG N, FONG YC *et al*.: Inter-

acting influences of pregnancy and corneal injury on rabbit lacrimal gland immunoarchitecture and function. *Invest Ophtalmol Vis Sci* 2006; 47: 1368-75.

24. STEINFELD S, ROMMES S, FRANÇOIS C *et al*.: Big prolactin 60kDa is overexpressed in salivary glandular epithelial cells from patients with Sjögren's syndrome. *Lab Invest* 2000; 80: 239-47.
25. MIRCHEFF A, WANG Y, DE SAINT JEAN M *et al*.: Mucosal immunity and self-tolerance in the ocular surface system. *The Ocular Surface* 2005; 3: 182-93.
26. STEINFELD S, MAHO A, CHABOTEAUX C *et al*.: Prolactin up-regulates cathepsin B and D expression in minor salivary glands of patients with Sjögren's syndrome. *Lab Invest* 2000; 11: 1711-20.
27. ADAMS KM, NELSON JL: Microchimerism: an investigative frontier in autoimmunity and transplantation. *JAMA* 2004; 291: 1127-31.
28. ARACTINGI S, SIBILIA J, MEIGNIN V *et al*.: Presence of microchimerism in labial salivary glands in systemic sclerosis but not in Sjögren's syndrome. *Arthritis Rheum* 2002; 46: 1039-43.
29. CARLUCCI F, PRIORI R, VALESINI G: Microchimerism in Sjögren's syndrome. *Rheumatology* 2003; 42: 486-7.
30. ENDO Y, NEGISHI I, ISHIKAWA O: Possible contribution of microchimerism to the pathogenesis of Sjögren's syndrome. *Rheumatology* 2002; 41: 490-5.