Menstrual and Reproductive Characteristics of Patients with Primary Sjogren's Syndrome: A 7-year Single-center Retrospective Study

Ying-zi ZHU, Ji-xin ZHONG#, Ling-li DONG#
Department of Rheumatology and Immunology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China

[Abstract] Objective: Primary Sjogren's syndrome (pSS) is a systemic autoimmune disease that mainly affects the exocrine gland, especially in women. Currently, the results of studies on the menstruation or fertility of pSS patients remain controversial. This study aimed to examine the menstrual and reproductive characteristics of pSS patients. **Methods:** Clinical data of 449 pSS patients who were admitted to Tongji Hospital in Hubei, China, from January 2015 to November 2021 were obtained and their menstrual and reproductive information analyzed. In addition, the clinical features of pSS patients with premenopausal or postmenopausal onset were compared. **Results:** The spontaneous abortion rate of pSS patients was not higher than the reported rate of the general population and that the age of menarche, menstrual cycle, and menstrual period of pSS patients did not significantly differ from those reported in the general population; however, early menopause seemed to be more common in pSS patients. Skin involvement (27.96% *vs.* 15.00%, *P*=0.005) and hyperglobulinemia (10.64% *vs.* 4.16%, *P*=0.033) were more common in patients with premenopausal pSS onset, but patients with postmenopausal onset had a significantly greater incidence of interstitial lung disease (32.50% *vs.* 17.02%, *P*=0.0004). Also, erythropenia (47.00% *vs.* 31.25%, *P*=0.002), hypoalbuminemia (19.49% *vs.* 8.22%, *P*=0.0009), and prevalence of high hypersensitive C-reactive protein levels (21.67% *vs.* 10.94%, *P*=0.005) were more common in pSS patients with postmenopausal onset. Notably, the rate of abnormal pregnancy was significantly greater in patients with premenopausal onset (9.72% *vs.* 2.50%, *P*=0.011). **Conclusion:** Patients with pSS onset before or after menopause may have different risks in pulmonary involvement and laboratory manifestations.

Key words: primary Sjogren's syndrome; menstruation; fertility; clinical features

Primary Sjogren's syndrome (pSS) is a systemic autoimmune disease that occurs mainly in middle-aged women and affects the exocrine glands (mainly the salivary and lacrimal glands) to cause severe dryness of the oral and ocular mucosal surface[1]. The clinical manifestation of pSS is heterogeneous, with symptoms ranging from mild dryness to systemic effects[2]. Multiple clinical techniques, including autoantibody tests, imaging techniques, and pathological biopsies, have been used to diagnose and evaluate pSS[3].

PSS also influences the fertility and menstruation of patients. Some studies reported that the spontaneous abortion rate and premature birth rate in pregnant women with pSS are greater than those in the normal pregnant population[4, 5] and that the normal delivery frequency of healthy women is significantly greater than that of pSS women[6, 7]. An international cooperative case-control study found that pSS patients have reduced estrogen levels and an older age of menarche as well as reduced cumulative times of menstruation[8]; moreover, the susceptibility of women to pSS is positively correlated with an irregular menstrual cycle[9]. However, other studies suggested no significant associations between pSS and the overall fertility rate, preterm birth, spontaneous abortion, or induced abortion, nor between the presence of autoantibodies and the preterm birth rate[10, 11]. Similarly, it was also reported that there is no significant difference in the age of menopause onset between pSS patients and healthy controls[12, 13]. Given the controversy that exists in terms of the fertility and menstruation of pSS patients, further analysis of these characteristics of pSS patients will contribute to a better understanding of the complexity of pSS.

Ying-zi ZHU, E-mail: zhuyingzi2018@126.com
#Corresponding authors, Ling-li DONG, E-mail: tjhdongll @163.com; Ji-xin ZHONG, E-mail: Zhongjixin620@163. com

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11596-022-2675-4) contains supplementary material, which is available to authorized users.

The incidence of spontaneous abortion among women of childbearing age in China is 5.04%–13.60%, and the incidence in other areas is different[14–16]. The induced abortion rate of Chinese women can be as high as 26.50%–38.77%[17–20]. Meanwhile, the infertility rate of Chinese women of childbearing age ranges from 9.00% to 25.00%, and it increases with age[21–23]. Although the rate of premature menopause or early menopause in Chinese women is not known, it was reported that about 5% of women experience early menopause (menopause onset at 40–45 years old) and 1%–3.8% of women experience premature menopause (menopause onset at <40 years old)[24–26]. However, there are few studies on the menstrual and reproductive information of pSS patients in China. Therefore, research on the menstrual and reproductive characteristics of pSS patients with a relatively large sample size is of great significance.

1 MATERIALS AND METHODS

1.1 Patients

By retrieving their electronic medical records, female pSS patients hospitalized at the Department of Rheumatology and Immunology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China, from January 2015 to November 2021 were included in this study. Patients without complete records of menstruation and fertility history were excluded. All patients were reassessed to meet the 2016 American College of Rheumatology/European League Against Rheumatism classification criteria for pSS[27]. All patients signed an informed consent at the time of admission. This study was approved by the Institutional Review Board of Tongji Medical College, Huazhong University of Science and Technology, and conformed to the provisions of the Declaration of Helsinki.

1.2 Clinical Information

Demographic data, medical history, laboratory indicators, imaging indicators, and pathological results were retrospectively collected. Menstrual and reproductive information, including age of menarche, menstrual cycle, menstrual period, age of menopause, gravidity, times of induced abortion, times of spontaneous abortion, and times of stillbirth, infertility, etc., was obtained. For clinical manifestations, xerostomia, xerophtalmia, and symptoms of Raynaud's disease, joint muscle symptoms (arthralgia, muscle pain, morning stiffness, dyskinesia, deformation, and joint necrosis), skin symptoms (rash, edema, erythema nodosum, itching, purpura, subcutaneous bleeding, ecchymosis, etc.), interstitial lung disease (diagnosed by high-resolution computed tomography), kidney symptoms (proteinuria, hypokalemia, and tubular acidosis), autoimmune hepatitis, hematological system symptoms (hypocytosis, gingival or nasal bleeding), and neurological symptoms (dizziness, headache, pain and numbness in fingers, lips, or tongue tip, and finger twitching) were recorded. Laboratory indicators (including autoantibody) levels, data of Schimer's test, salivary gland single photon emission computed tomography (SPECT) and histopathological analyses of labial gland biopsy were also collected.

1.3 Statistical Analysis

The values of laboratory indicators were converted into measurement data. Pearson's chi-squared test or Fisher's exact test was used to compare the laboratory indicators and clinical characteristics between different subgroups. Count data were presented in numerical and percentage forms. A *P*-value less than 0.05 indicates statistical significance.

2 RESULTS

2.1 Clinical and Gynecological Characteristics of pSS Patients

A total of 449 female patients with pSS, mostly middle-aged (46.18±11.90 years old), were enrolled in this study (table 1). Of these, 257 patients (57.24%) complained of xerostomia, 216 patients (48.11%) complained of dry eye, and 143 patients (82.65% of the patients who underwent the Schirmer's test) were diagnosed with xerophtalmia. In addition to oral and ocular symptoms, arthritis and rash were the most common symptoms. Most patients were in the active

Table 1 The clinical manifestations of pSS patients

	Mean (±SD) or *n* (percentage)
Age (*n*=449)	46.18±11.90 (years old)
Xerostomia (*n*=449)	257 (57.24%)
Dry eye (*n*=449)	216 (48.11%)
Raynaud's sign (*n*=449)	42 (9.35%)
Arthralgia (*n*=449)	213 (47.43%)
Parotitis (*n*=449)	16 (3.56%)
Hyperglobulinemia (*n*=449)	40 (8.90%)
Rash or purpura (*n*=449)	110 (24.49%)
ILD (*n*=449)	95 (21.20%)
AIH (*n*=449)	24 (5.34%)
RTA (*n*=449)	16 (3.56%)
Hypocytosis (*n*=449)	70 (15.59%)
PN (*n*=449)	30 (6.68%)
Anti-SSA (*n*=449)	428 (95.32%)
Anti-SSB (*n*=449)	249 (55.45%)
SPECT (*n*=313)	281 (89.77%)
Schirmer's test (*n*=173)	143 (82.65%)
Labial gland biopsy (*n*=233)	194 (83.26%)
ESSDAI score ≥4 (*n*=449)	344 (76.78%)

pSS: primary Sjogren's syndrome; ILD: interstitial lung disease; AIH: autoimmune hepatitis; RTA: renal tubular acidosis; PN: peripheral neuropathy; SPECT: single photon emission computed tomography of salivary glands; ESSDAI: European League Against Rheumatism Sjogren's Syndrome Disease Activity Index; SD: standard deviation

stage of pSS, and the involvement of lung and blood system was more frequent than that of liver and kidney. Anti-SSA was the most prominent autoantibody in pSS patients, and the positive rate of SPECT was roughly consistent with that of Schirmer's test.

Subsequently, the menstrual and reproductive characteristics of these female patients were analyzed (table 2). Most of the pSS patients experienced menarche at the normal age, and the abnormal cases showed delayed menarche. Similarly, some patients have demonstrated prolonged menstrual periods or menstrual cycles. However, for menopausal abnormalities, early menopause was more frequently observed. Spontaneous abortion was the main pregnancy abnormality in pSS patients.

Table 2 The menstrual and reproductive characteristics of pSS patients

	Subgroup		*n* (percentage)
Menstrual history			
Age of menarche (years old) (*n*=449)	Earlier menarche	(<11)	0 (0.00%)
	Normal menarche	(11–16)	432 (96.21%)
	Delayed menarche	(>16)	17 (3.79%)
Menstrual cycle (days) (*n*=449)	Shorter cycle	(<21)	0 (0.00%)
	Normal menstrual cycle	(21–35)	442 (98.44%)
	Prolonged cycle	(>35)	7 (1.56%)
Menstrual period (days) (*n*=449)	Shorter menstrual period	(<2)	0 (0.00%)
	Normal menstrual period	(2–8)	445 (99.11%)
	Prolonged menstrual period	(>8)	4 (0.89%)
Age of menopause (years old) (*n*=270)[#]	Premature menopause	<40	2 (0.74%)
	Early menopause	(40–45)	24 (8.89%)
	Normal menopause	>45	244 (90.37%)
Reproductive history (*n*=449)			
Abnormal pregnancy	Spontaneous abortion		31 (6.90%)[†]
	Stillbirth		3 (0.66%)[†]
	Infertility		4 (0.89%)
Without abnormal pregnancy			414 (92.20%)

[#]: 179 patients were not menopausal. [†]Three patients with a history of spontaneous abortion also had a history of stillbirth. pSS: primary Sjogren's syndrome

2.2 Abnormal Pregnancy Was Not Significantly Associated with Clinical Features of pSS

Next, we compared the clinical characteristics of 35 pSS patients with a history of abnormal pregnancy (including spontaneous abortion, stillbirth, or infertility) and 414 patients without. In general, there was no significant difference in the clinical symptoms or laboratory indicators between the two groups (table 3). In addition, there was no significant difference in the incidence of impaired salivary gland function, positive rate of autoantibodies, or lymphocyte infiltration of the labial gland between the two groups. Also, no significant difference in organ involvement or laboratory indicators between 146 patients with a history of induced abortion and those with a history of spontaneous abortion or without a history of abnormal pregnancy was found, except that the pSS patients with a history of induced abortion had a lower rate of serum complement C3 reduction (data not shown).

2.3 pSS Patients with Premenopause or Postmenopause Onset had Different Clinical Features

Further, we compared the clinical characteristics of 329 pSS patients with premenopausal onset and 120 with postmenopausal onset. First, the incidence of xerostomia, xerophthalmia, renal tubular acidosis, autoimmune hepatitis, parotid gland enlargement, arthralgia, and peripheral neuropathy did not differ significantly between the pre- and postmenopausal onset groups. However, the premenopausal onset group had a significantly increased incidence of rash or purpura (27.96% *vs.* 15.00%, *P*=0.005) and hyperglobulinemia (10.64% *vs.* 4.16%, *P*=0.033), while the postmenopausal onset group had a significantly higher incidence of ILD (32.50% *vs.* 17.02%, *P*=0.0004) (table 4). Additionally, hypoalbuminemia (19.49% *vs.* 8.22%, *P*=0.0009) and erythropenia (47.00% *vs.* 31.25%, *P*=0.002) were more common in the patients with postmenopausal onset. There was no difference between the two groups in terms of liver transaminase levels, renal related indicators, Ig subclass, or complement levels. Although the incidence of an elevated level of hsCRP was significantly common in the postmenopausal onset group (21.67% *vs.* 10.94%, *P*=0.005), there was no significant association between premenopausal or postmenopausal onset of pSS and ESSDAI score, and no difference in the positive rate of autoantibodies and lymphocyte infiltration in the labial glands were observed between the two groups.

Besides, the menstrual and reproductive characteristics of the postmenopausal patients with premenopausal onset were compared. The incidence rates of delayed menarche, prolonged menstrual cycle, prolonged menstrual period, and early menopause were not significantly different between the patients

Table 3 Comparison of clinical manifestations of pSS patients with and those without an abnormal pregnancy

	With abnormal pregnancy history (*n*=35)	Without abnormal pregnancy history (*n*=414)	*P* value
Xerostomia (*n*=449)	20 (57.14%)	237 (57.25%)	0.991
Dry eye (*n*=449)	14 (40.00%)	202 (48.79%)	0.317
Raynaud sign (*n*=449)	2 (5.71%)	40 (9.66%)	0.760
Arthralgia (*n*=449)	17 (48.57%)	196 (47.34%)	0.889
Parotitis (*n*=449)	2 (5.71%)	14 (3.38%)	0.359
Hyperglobulinemia (*n*=449)	4 (11.42%)	36 (8.69%)	0.538
Rash or purpura (*n*=449)	10 (28.57%)	100 (24.15%)	0.560
ILD (*n*=449)	8 (23.52%)	87 (21.01%)	0.730
AIH (*n*=449)	0 (0.00%)	24 (5.79%)	0.242
RTA (*n*=449)	2 (5.71%)	14 (3.38%)	0.359
Hypocytosis (*n*=449)	7 (20.00%)	63 (15.21%)	0.454
PN (*n*=449)	3 (8.57%)	27 (6.52%)	0.720
Leukopenia (*n*=438)	9 (26.47%)	69 (17.07%)	0.169
Neutropenia (*n*=437)	4 (11.76%)	42 (10.42%)	0.771
Lymphopenia (*n*=437)	8 (23.52%)	58 (14.39%)	0.153
Erythropenia (*n*=437)	16 (47.05%)	139 (34.49%)	0.141
Hypohemoglobin (*n*=437)	15 (44.11%)	121 (30.02%)	0.088
Thrombocytopenia (*n*=437)	6 (17.64%)	49 (12.15%)	0.415
Elevated ALT (*n*=435)	2 (5.71%)	43 (10.75%)	0.561
Elevated AST (*n*=431)	3 (8.57%)	58 (14.65%)	0.450
Elevated TP (*n*=434)	9 (25.71%)	90 (22.55%)	0.669
Hypoalbuminemia (*n*=434)	5 (14.28%)	44 (11.02%)	0.575
Elevated TBil (*n*=431)	1 (2.85%)	5 (1.26%)	0.400
Elevated TCHO (*n*=431)	0 (0.00%)	34 (8.58%)	0.096
Elevated BUN (*n*=432)	2 (5.88%)	15 (3.76%)	0.635
Elevated Cr (*n*=433)	1 (2.94%)	36 (9.02%)	0.341
Elevated UA (*n*=432)	5 (14.70%)	42 (10.55%)	0.399
Elevated ESR (*n*=449)	17 (48.57%)	209 (50.85%)	0.796
Elevated HsCRP (*n*=437)	4 (11.76%)	58 (14.39%)	0.803
Elevated IgG (*n*=449)	20 (57.14%)	250 (60.38%)	0.707
Elevated IgA (*n*=437)	2 (5.88%)	71 (17.61%)	0.078
Elevated IgM (*n*=435)	2 (5.88%)	44 (10.97%)	0.560
Decreased C3 (*n*=422)	12 (35.29%)	84 (21.64%)	0.069
Decreased C4 (*n*=411)	2 (6.06%)	20 (5.29%)	0.693
Anti-SSA (*n*=449)	34 (97.14%)	394 (95.16%)	1.000
Anti-SSB (*n*=449)	17 (48.57%)	232 (56.03%)	0.393
SPECT (*n*=313)	25 (100.0%)	256 (88.88%)	0.091
Schirmer's test (*n*=173)	9 (81.81%)	134 (93.70%)	1.000
Labial gland biopsy (*n*=233)	16 (84.21%)	178 (83.18%)	1.000
ESSDAI score ≥4 (*n*=449)	29 (82.86%)	315 (76.27%)	0.376

pSS: primary Sjogren's syndrome; ILD: interstitial lung disease; AIH: autoimmune hepatitis; RTA: renal tubular acidosis; PN: peripheral neuropathy; ALT: alanine aminotransferase; AST: aspartate amino transferase; TP: total serum protein; TBil: total bilirubin; TCHO: total cholesterol; BUN: blood urea nitrogen; Cr: creatinine; UA: uric acid; ESR: erythrocyte sedimentation rate; HsCRP: high-sensitivity C-reactive protein; SPECT: single photon emission computed tomography of salivary glands; ESSDAI: European League Against Rheumatism Sjogren's Syndrome Disease Activity Index. The data were analyzed by Pearson's chi-squared test or Fisher's exact test. $P<0.05$ indicates a significant difference.

with premenopausal and those with postmenopausal pSS onset. However, it should be noted that the rate of abnormal pregnancy was significantly greater among the patients with premenopausal onset (9.72% *vs.* 2.50%, $P=0.011$) (table 5).

Additionally, we explored whether the clinical symptoms and laboratory indicators are influenced by a history of early menopause. There was no significant difference in these indicators between the patients with and those without early menopause, except for a higher incidence of elevated hsCRP and positive anti-SSB antibodies in normal menopause patients (supplementary table 1).

3 DISCUSSION

Autoimmune diseases have a unique pathogenesis in obstetrics and gynecology. First, chronic inflammation impinges on the normal function of the hypothalamic-pituitary-ovarian axis, leading to the abnormal release of gonadotropin-releasing hormone and gonadotropin[28]. Second, autoimmunity may

Table 4 Comparison between pSS patients with premenopausal and those with postmenopausal onset

	Premenopausal onset (*n*=329)	Postmenopausal onset (*n*=120)	*P* value
Xerostomia (*n*=449)	188 (57.49%)	69 (57.50 %)	0.946
Dry eye (*n*=449)	157 (47.72%)	59 (49.16%)	0.786
Raynaud sign (*n*=449)	35 (10.63%)	7 (5.83%)	0.122
Arthralgia (*n*=449)	160 (48.63%)	53 (44.16%)	0.402
Parotitis (*n*=449)	14 (4.25%)	2 (1.66%)	0.256
Hyperglobulinemia (*n*=449)	35 (10.64%)	5 (4.16%)	0.033*
Rash or purpura (*n*=449)	92 (27.96%)	18 (15.00%)	0.005**
ILD (*n*=449)	56 (17.02%)	39 (32.50%)	0.0004***
AIH (*n*=449)	20 (6.07%)	4 (3.33%)	0.252
RTA (*n*=449)	11 (3.34%)	5 (4.17%)	0.774
PN (*n*=449)	18 (5.47%)	12 (10.00%)	0.089
Leukopenia (*n*=438)	62 (19.31%)	16 (13.67%)	0.172
Neutropenia (*n*=437)	37 (11.56%)	9 (7.69%)	0.470
Lymphopenia (*n*=437)	52 (16.25%)	14 (11.96%)	0.268
Erythropenia (*n*=437)	100 (31.25%)	55 (47.00%)	0.002**
Hypohemoglobin (*n*=437)	94 (29.37%)	42 (35.89%)	0.192
Thrombocytopenia (*n*=437)	39 (12.19%)	16 (13.67%)	0.678
Elevated ALT (*n*=435)	34 (10.72%)	11 (9.32%)	0.669
Elevated AST (*n*=431)	44 (14.01%)	17 (14.52%)	0.891
Elevated TP (*n*=434)	79 (25.00%)	20 (16.94%)	0.075
Hypoalbuminemia (*n*=434)	26 (8.22%)	23 (19.49%)	0.0009***
Elevated TBil (*n*=431)	5 (1.58%)	1 (0.86%)	1.000
Elevated TCHO (*n*=431)	20 (6.38%)	14 (11.86%)	0.060
Elevated BUN (*n*=432)	12 (3.80%)	5 (4.27%)	0.786
Elevated Cr (*n*=433)	22 (6.98%)	15 (12.71%)	0.058
Elevated UA (*n*=432)	34 (10.79%)	13 (11.11%)	0.925
Elevated ESR (*n*=449)	160 (49.07%)	66 (55.00%)	0.267
Elevated HsCRP (*n*=449)	36 (10.94%)	26 (21.67%)	0.005**
Elevated IgG (*n*=449)	205 (62.31%)	65 (54.16%)	0.119
Elevated IgA (*n*=437)	53 (16.66%)	20 (16.80%)	0.972
Elevated IgM (*n*=437)	34 (10.72%)	12 (10.16%)	0.867
Decreased C3 (*n*=422)	73 (23.77%)	23 (20.00%)	0.410
Decreased C4 (*n*=377)	15 (4.98%)	7 (6.36%)	0.582
Anti-SSA (*n*=449)	317 (96.35%)	111 (92.50%)	0.087
Anti-SSB (*n*=449)	185 (56.23%)	64 (53.33%)	0.585
SPECT (*n*=313)	207 (91.19%)	74 (86.04%)	0.180
Schirmer's Test (*n*=173)	91 (79.13%)	52 (89.65%)	0.084
Labial gland biopsy (*n*=233)	139 (82.25%)	55 (85.93%)	0.501
ESSDAI score ≥4 (*n*=449)	252 (76.82%)	92 (76.66%)	0.971

pSS: primary Sjogren's syndrome; ALT: alanine aminotransferase; AST: aspartate amino transferase; TP: total serum protein; TBil: total bilirubin; TCHO: total cholesterol; BUN: blood urea nitrogen; Cr: creatinine; UA: uric acid; ESR: erythrocyte sedimentation rate; HsCRP: high-sensitivity C-reactive protein; SPECT: single photon emission computed tomography of salivary glands; ESSDAI: European League Against Rheumatism Sjogren's Syndrome Disease Activity Index. The data were analyzed by Pearson chi-squared test or Fisher's exact test. $P<0.05$ indicates a significant difference. $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$

Table 5 Menstrual and reproductive characteristics of pSS patients with premenopausal or postmenopausal onset

	Premenopausal onset (*n*=329)	Postmenopausal onset (*n*=120)	*P* value
Menarche delay (*n*=449)	13 (3.95 %)	4 (3.33%)	1.000
Prolonged menstrual cycle (*n*=449)	7 (2.13%)	0 (0.00%)	0.197
Prolonged menstruation (*n*=449)	4 (1.22%)	0 (0.00%)	0.577
Premature or early menopause (*n*=270)	16 (10.45%)	10 (8.54%)	0.598
Abnormal pregnancy (*n*=449)	32 (9.72%)	3 (2.50%)	0.011*

pSS: primary Sjogren's syndrome. The data were analyzed by Pearson's chi-squared test or Fisher's exact test. $P<0.05$ indicates a significant difference. $^{*}P<0.05$

be associated with the production of anti-ovarian antibodies and subsequent autoimmune ovaritis, which induce ovarian tissue damage and reduce the ovarian reserve[29]. From this single-center study, the pSS patients did not have a higher abortion rate, including spontaneous and induced abortion, than the general

population, and no definitive association between abortion history and the progression of pSS was found. Also, there was no difference in the positive rates of anti-SSA and anti-SSB in the different subgroups of reproductive history, although it has been reported that the positivity of these autoantibodies is associated with fetal congenital heart block[30, 31]. In this study, the infertility rates among the pSS patients were less than those reported in the general population; therefore, a trial with a larger sample size is needed to confirm these findings. The age of menarche, menstrual cycle, and period length of most pSS patients did not significantly differ from those reported in the general population. However, the proportion of pSS patients that experienced early menopause was greater than the reported proportion of the general population (8.89% *vs.* 5%), implying that the ovarian function of pSS patients may be affected by autoimmune disease.

Although pSS has been reported to have no special effect on menopause[12, 13, 32], our study found that the relationship between the onset of pSS and the timing of menopause may affect the clinical characteristics of patients. The incidence of ILD was greater in the pSS patients with postmenopausal onset, perhaps because of the regulatory role of sex hormones in lung inflammation. As one of the most important hormones, estrogen can effectively protect secretory acinar cells, and estrogen deficiency during menopause may specifically accelerate the apoptosis of exocrine acinar cells[33]. Under normal physiological conditions, estrogen has anti-inflammatory effects in premenopausal women[34]. After menopause, the estrogen level is relatively reduced, and its mediated protective effect is weakened, which may promote lung inflammation in patients, and the interaction between estrogen and its receptor also has been described in studies on lung cancer and coronavirus disease 2019[35–38]. Moreover, patients with postmenopausal onset have a relatively poor basic lung function. It is noteworthy that the spontaneous abortion rates of pSS patients with premenopausal onset were significantly higher, which may indicate that pSS patients with premenopausal onset are more prone to abnormal pregnancy events.

The limitation of this study is that the classification of system involvement in our study is general, and there was no specific analysis of the included symptoms or diseases. In addition, for the analysis of menstrual history, the sample size of the abnormal group was too small for further analysis; therefore, a larger sample size is needed to study this issue further.

In conclusion, our study demonstrated that pSS patients did not have a higher abortion rate than the general population. Additionally, patients with pSS experienced early menopause more frequently than the general population. Furthermore, the incidence of ILD was greater in the pSS patients with postmenopausal onset, and the incidence of abnormal pregnancy was greater in the pSS patients with premenopausal onset. This study provides valuable information for the analysis of the menstrual and reproductive characteristics of the pSS population in China.

Acknowledgments

We are very grateful to all the staff working in the Department of Medical Records of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, for their help in this study.

Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Ling-li DONG is a member of the Editorial Board for [Current Medical Science]. The paper was handled by other editors and has undergone rigorous peer review process. Author Ling-li DONG was not involved in the journal's review of, or decisions related to, this manuscript.

REFERENCES

1 Shiboski CH, Shiboski SC, Seror R, *et al*. 2016 American College of Rheumatology/European League Against Rheumatism Classification Criteria for Primary Sjögren's Syndrome: A Consensus and Data-Driven Methodology Involving Three International Patient Cohorts. Arthritis Rheumatol, 2017,69(1):35-45
2 Brito-Zerón P, Baldini C, Bootsma H, *et al*. Sjögren syndrome. Nat Rev Dis Primers, 2016,2:16047
3 Fox RI. Sjögren's syndrome. Lancet, 2005,366(9482): 321-331
4 De Carolis S, Salvi S, Botta A, *et al*. The impact of primary Sjogren's syndrome on pregnancy outcome: our series and review of the literature. Autoimmun Rev, 2014,13(2):103-107
5 Ballester C, Grobost V, Roblot P, *et al*. Pregnancy and primary Sjögren's syndrome: management and outcomes in a multicentre retrospective study of 54 pregnancies. Scand J Rheumatol, 2017,46(1):56-63
6 Hussein SZ, Jacobsson LT, Lindquist PG, *et al*. Pregnancy and fetal outcome in women with primary Sjogren's syndrome compared with women in the general population: a nested case-control study. Rheumatology (Oxford), 2011,50(9):1612-1617
7 Elliott B, Spence AR, Czuzoj-Shulman N, *et al*. Effect of Sjögren's syndrome on maternal and neonatal outcomes of pregnancy. J Perinat Med, 2019,47(6):637-642
8 McCoy SS, Sampene E, Baer AN. Association of Sjögren's Syndrome With Reduced Lifetime Sex Hormone Exposure: A Case-Control Study. Arthritis Care Res (Hoboken), 2020,72(9):1315-1322
9 Lu MC, Hsieh MC, Koo M, *et al*. Risk of Sjögren's syndrome in Taiwanese female adults with irregular menstrual cycles: a population-based case-control study. Rheumatol Int, 2016,36(1):155-160
10 Upala S, Yong WC, Sanguankeo A. Association between primary Sjögren's syndrome and pregnancy complications: a systematic review and meta-analysis. Clin Rheumatol, 2016,35(8):1949-1955

11 Haga HJ, Gjesdal CG, Irgens LM, *et al*. Reproduction and gynaecological manifestations in women with primary Sjögren's syndrome: a case-control study. Scand J Rheumatol, 2005,34(1):45-48
12 Pasoto SG, Augusto KL, Alvarenga JC, *et al*. Cortical bone density and thickness alterations by high-resolution peripheral quantitative computed tomography: association with vertebral fractures in primary Sjögren's syndrome. Rheumatology (Oxford), 2016,55(12):2200-2211
13 Balarini GM, Zandonade E, Tanure L, *et al*. Serum calprotectin is a biomarker of carotid atherosclerosis in patients with primary Sjögren's syndrome. Clin Exp Rheumatol, 2016,34(6):1006-1012
14 Zheng D, Li C, Wu T, *et al*. Factors associated with spontaneous abortion: a cross-sectional study of Chinese populations. Reprod Health, 2017,14(1):33
15 Hu CY, Yang XJ, Hua XG, *et al*. Risk factors for spontaneous abortion from a prevention perspective in rural China: a population-based follow-up study. J Matern Fetal Neonatal Med, 2021,34(16):2583-2591
16 Zeng LX, Yan H, Chen ZJ. Study on the current status and risk factors of spontaneous abortion of women at reproductive age in rural areas of Xianyang district, Shaanxi province. Zhonghua Liu Xing Bing Xue Za Zhi (Chinese), 2007,28(1):19-23
17 Su Y, Xie X, Zhou Y, *et al*. Association of induced abortion with hypertensive disorders of pregnancy risk among nulliparous women in China: a prospective cohort study. Sci Rep, 2020,10(1):5128
18 Wang C. Induced abortion patterns and determinants among married women in China: 1979 to 2010. Reprod Health Matters, 2014,22(43):159-168
19 Tang L, Wu S, Liu D, *et al*. Repeat Induced Abortion among Chinese Women Seeking Abortion: Two Cross Sectional Studies. Int J Environ Res Public Health, 2021,18(9):4446
20 Wang X, Wu J, Li Y, *et al*. Changes in the Prevalence of Induced Abortion in the Floating Population in Major Cities of China 2007-2014. Int J Environ Res Public Health, 2019,16(18):3305
21 Zhou Z, Zheng D, Wu H, *et al*. Epidemiology of infertility in China: a population-based study. Bjog, 2018,125(4):432-441
22 He Y, Zheng D, Shang W, *et al*. Prevalence of oligomenorrhea among women of childbearing age in China: A large community-based study. Womens Health (Lond), 2020,16:1745506520928617
23 Liang S, Chen Y, Wang Q, *et al*. Prevalence and associated factors of infertility among 20-49 year old women in Henan Province, China. Reprod Health, 2021,18(1):254
24 Honigberg MC, Zekavat SM, Aragam K, *et al*. Association of Premature Natural and Surgical Menopause With Incident Cardiovascular Disease. Jama, 2019,322(24):2411-2421
25 Honigberg MC, Patel AP, Lahm T, *et al*. Association of premature menopause with incident pulmonary hypertension: A cohort study. PloS One, 2021,16(3):e0247398
26 Shifren JL, Gass ML. The North American Menopause Society recommendations for clinical care of midlife women. Menopause, 2014,21(10):1038-1062
27 Shiboski CH, Shiboski SC, Seror R, *et al*. 2016 American College of Rheumatology/European League Against Rheumatism classification criteria for primary Sjögren's syndrome: A consensus and data-driven methodology involving three international patient cohorts. Ann Rheum Dis, 2017,76(1):9-16
28 Harbuz MS, Chover-Gonzalez AJ, Jessop DS. Hypothalamo-pituitary-adrenal axis and chronic immune activation. Ann N Y Acad Sci, 2003,992:99-106
29 LaBarbera AR, Miller MM, Ober C, *et al*. Autoimmune etiology in premature ovarian failure. Am J Reprod Immunol Microbiol, 1988,16(3):115-122
30 Madhusudan D, Raju A, Vijaya N. Correlation of Maternal Autoantibodies with Fetal Congenital Heart Block. J Obstet Gynaecol India, 2016,66(Suppl 1):112-116
31 Anami A, Fukushima K, Takasaki Y, *et al*. The predictive value of anti-SS-A antibodies titration in pregnant women with fetal congenital heart block. Mod Rheumatol, 2013,23(4):653-658
32 Augusto KL, Bonfa E, Pereira RM, *et al*. Metabolic syndrome in Sjögren's syndrome patients: a relevant concern for clinical monitoring. Clin Rheumatol, 2016,35(3):639-647
33 Kirshenbaum M, Orvieto R. Premature ovarian insufficiency (POI) and autoimmunity-an update appraisal. J Assist Reprod Genet, 2019,36(11):2207-2215
34 Straub RH. The complex role of estrogens in inflammation. Endocr Rev, 2007,28(5):521-574
35 Al-Lami RA, Urban RJ, Volpi E, *et al*. Sex Hormones and Novel Corona Virus Infectious Disease (COVID-19). Mayo Clin Proc, 2020,95(8):1710-1714
36 Honma N, Hosoi T, Arai T, *et al*. Estrogen and cancers of the colorectum, breast, and lung in postmenopausal women. Pathol Int, 2015,65(9):451-459
37 Hsu LH, Chu NM, Kao SH. Estrogen, Estrogen Receptor and Lung Cancer. Int J Mol Sci, 2017,18(8)
38 Spratt DI, Buchsbaum RJ. COVID-19 and Hypercoagulability: Potential Impact on Management with Oral Contraceptives, Estrogen Therapy and Pregnancy. Endocrinology, 2020,161(12): bqaa121

(Received Jan. 10, 2022; accepted Mar. 2, 2022)