Obstetric and gynaecological profile in patients with primary Sjögren's syndrome

Fotini N Skopouli, Silvia Papanikolaou, Vasiliki Malamou-Mitsi, Nikolaos Papanikolaou, Haralampos M Moutsopoulos

Abstract

Objective—To describe the effects of Sjögren's syndrome (SS) on the fertility, parity and sexual activity as well as investigating the aetiopathology of dyspareunia in female patients.

Methods—Fifty one female patients with primary SS (pSS) and 57 healthy controls were interviewed concerning their past gynaecological, obstetric and sexual history and underwent a complete gynaecological examination. Punch biopsy of the vagina was performed in six patients and one healthy individual. In addition, the vaginal tissue was evaluated following hysterectomy in two patients with pSS.

Results—No differences were observed in fertility, parity or reproductive success rate between patients and controls. Atrophy of the external genitalia and production of cervical mucus in both patients and controls correlated with age and menopause, but not with other clinical or serological pSS manifestations. Dyspareunia was observed in 40% of the patients during the premenopause period compared with 3% observed in controls. Half of the patients, however, had an obvious aetiology for dyspareunia (trauma or inflammation) not related to pSS. The histological picture of the patients' vaginal tissue revealed perivascular infiltration. Finally, pSS patients appeared to have a similar intercourse frequency with the controls. However, unlike that observed in controls, the intercourse frequency did not diminish with age nor with the presence of dyspareunia. **Conclusion**—The fertility, parity and sexual activity of pSS patients does not appear to differ from that of the healthy population. Dyspareunia is a frequent symptom in these patients and local perivascular inflammation may contribute to the expression of this manifestation.

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Systemic autoimmune rheumatic disorders which primarily afflict women, may interfere with the normal reproductive function of the patients. This is supported by reports that infertility, spontaneous abortions and stillbirths are more common in patients with systemic lupus erythematosus (SLE) and scleroderma than in age matched controls.^{1–6}

Conversely, pregnancy has been associated with both negative and positive alterations in the disease status. Thus pregnancy in SLE may lead to an exacerbation of the disease while in rheumatoid arthritis (RA) pregnancies may induce disease remission.^{7,8}

These issues have not been carefully addressed in primary Sjögren's syndrome (pSS), an almost exclusively female disease.⁹ This may be related to the fact that pSS does not usually become clinically apparent until the fourth decade of life, an age in which child-bearing has been completed.

Despite the fact that pSS patients manifest problems with the external genitalia and often complain of dyspareunia,¹⁰ the pathobiology of this symptom has not been clarified. To our knowledge the study of Capriello *et al*¹¹ is the only one which combines clinical and histological findings in pSS patients.

In this study, we attempted to describe the obstetric, gynaecological and sexual profile of patients with pSS in addition to providing on evaluation of pathophysiology of dyspareunia in these patients.

Patients and methods

Fifty one female patients with primary Sjögren's syndrome who were followed at the outpatient rheumatology division of the Ioannina Medical School, Greece, were examined. In addition, 57 healthy, age matched women, including 47 staff members, as well as 10 individuals accompanying children admitted to hospital, were used as controls.

The patients, as well as the healthy women, answered a specific questionnaire which addressed the following: (1) age of menarche; (2) age of first sexual intercourse and frequency of intercourse at the time of evaluation; (3) libido and satisfaction; (4) use of contraceptive pills; (5) number of deliveries, spontaneous abortions, stillbirths, iatrogenic abortions; (6) age of menopause or cause of surgical uterus removal; (7) subjective complaints of dyspareunia, vaginal sensation of a foreign body, burning, itching or intolerance to antiseptics, and (8) frequency of vaginitis, cervicitis or Bartholin's cysts.

The fertility and parity, the adjusted fertility and parity and the reproductive success rates, as well as the number of spontaneous abortions, stillbirths and the infertility were evaluated in the two groups. Fertility rate is the average number of pregnancies per woman. Parity rate is the average number of

Department of Internal Medicine, School of Medicine, University of Ioannina, Greece
F N Skopouli

Department of Gynaecology, G Hatzikosta General Hospital, Ioannina, Greece
S Papanikolaou
N Papanikolaou

Department of Pathology, School of Medicine, University of Ioannina, Greece
V Malamou-Mitsi

Department of Pathophysiology, School of Medicine, National University of Athens, Greece
H M Moutsopoulos

Correspondence to: Dr H M Moutsopoulos, National University of Athens, Department of Pathophysiology, M Asias 76, Goudi, 115 27 Athens, Greece.

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pregnancies reaching 28 weeks per pregnant woman. Adjusted fertility and parity rates are corrected for years at risk for pregnancy. Success rate signifies the percentage of pregnancies yielding a viable infant. Spontaneous abortion is the spontaneous termination of pregnancy prior to 20 weeks' gestation. Stillbirth is the spontaneous termination of pregnancy after 24 weeks' gestation. Infertility is the lack of conception despite coitus without contraception.

From the examination of the external genitalia the following signs were noted: (1) atrophy or hypertrophy of the clitoris; (2) atrophy or ulcerations of the small and large labia; (3) atrophy, dryness, congestion, or ulceration of the vagina (atrophy was confirmed in vaginal smears by cytology and dryness was considered if no fluid was observed in the vaginal fornix); (4) atrophy, hypertrophy, nodules or ulcers of the cervix; and (5) atrophic or enlarged uterus with or without leiomyomas. Microscopic examination and culture of vaginal fluids was performed when infection was suspected. Cytological examination of vaginopancervical smears (PAP test) were performed on all women. The epithelial cellular morphology, the presence or absence of inflammation and the hormonal pattern compared with the age and menstrual history were evaluated by cytology. After informed consent, punch vaginal biopsy was performed in six patients and one healthy individual. The tissue was processed in the routine fashion, haematoxylin and eosin-stained slides were prepared and a histological diagnosis was rendered. In addition, the vaginal tissue from two patients who had hysterectomy for leiomyoma of the uterus was evaluated. All specimens were examined 'blind'.

The primary SS patient medical records were reviewed and the following clinical and laboratory data related to their disease status at the time of examination were collected: age, disease duration, presence of keratoconjunctivitis sicca (by positive Rose-Bengal staining on slit lamp examination) and xerostomia, parotid gland enlargement, Raynaud's phenomenon, arthritis, lymphadenopathy, splenomegaly, pulmonary involvement (by abnormal functional tests or decreased PO_2 levels on blood gas analysis),¹² kidney involvement (interstitial nephritis) (by urinalysis, creatinine levels and histology), myositis (by examination, histology), purpura (by examination), systemic vasculitis (by examination, histology), peripheral neuropathy (by examination, nerve conduction studies), RF (titre IgM, latex fixation), antinuclear antibodies (ANA) (pattern, titre, immunofluorescence), antibodies to Ro(SSA) and La(SSB) (counter-immunoelectrophoresis). The histopathological picture of the labiar minor salivary gland biopsies had been evaluated previously according to Tarpley's classification.¹³

STATISTICAL ANALYSIS

Descriptive analysis of different parameters in the two groups was carried out using

percentages and means. Comparison between groups was performed using Student's *t* test and contingency table analysis. Correlation within different parameters in the same group was carried out using simple regression analysis. Finally, the influence of age, menopause, disease duration and other parameters to different patient's signs and symptoms was tested using simple regression analysis and one factor analysis of variance (ANOVA).

Results

The mean age of patients with SS did not differ from that of controls (table 1). Four patients with SS and one healthy woman experienced 'early' menarche. Menstrual cycle abnormalities were reported by two patients with SS and six normal women. At the time of the study 31 of 51 patients with SS and 22 of 57 healthy controls were post menopausal. Seven patients with SS and three controls had undergone hysterectomy. The reported age at the beginning of menopause was similar in the two groups (table 1).

SS symptomatology began in 34 patients before the menopause and in 17 after the menopause. In 13 patients the symptomatology started around the time of the menopause (two years before or after).

Forty eight of 51 patients with SS reported a total of 207 pregnancies whereas 50 of 57 healthy women had 187 pregnancies. All the patients had at least one pregnancy before the beginning of disease symptoms. Fertility rate and adjusted fertility, parity rate and adjusted parity rate and reproductive success rate were similar in both groups (table 2). Two of the 51 patients reported that they had never experienced sexual intercourse. None of the patients with SS nor the controls ever used contraceptive pills or devices.

The number of fetal wastage, spontaneous abortions, stillbirths, premature infants as well as the caesarean sections were similar in patients and controls. Induced abortions, however, were more frequent in the patient group compared with controls ($p < 0.0005$) (table 3). No relation was found between RF, ANA, Ro(SSA), La(SSB) antibodies and fetal wastage or premature infants.

Patients and controls reported their first sexual experience at an age ranging from 17 to 35 years [mean 22 (SD 4.0)] and 14 to 35 years [21.63 (4.18)], respectively. The reported frequency of intercourse (times per week) in patients and controls was similar (fig 1). Seventy per cent of patients and 72% of controls reported libido. In both groups a positive correlation of libido and satisfaction was found ($p < 0.0001$). In the control group the intercourse frequency was positively correlated with libido ($p < 0.0005$) and negatively correlated with age ($p < 0.0001$) (fig 2), menopause ($p < 0.0006$) and dyspareunia ($p < 0.0006$). In the patient group, no correlation was found among intercourse frequency and the above parameters (fig 2). In addition, the intercourse frequency in the patient group was not related to disease duration.

Table 1 Menstrual cycle characteristics in patients with primary Sjögren's syndrome

No	Patients with primary Sjögren's syndrome 51	Controls 57
Age, mean (SD)	50.67 (10.99)	43.93 (15.01)
Early menarche	4	1
Menstrual cycle abnormalities	2	6
Menopause	31	22
Surgical menopause	7	3
Beginning of menopause (age)	48.66 (5.61)	47.78 (3.13)

Table 2 Fertility and parity in patients with primary Sjögren's syndrome

	Patients with primary Sjögren's syndrome	Controls
Number of pregnant individuals/Number of pregnancies	48/207	50/178
Fertility rate/adjusted fertility	4.3/4.5	3.6/4.0
Parity rate/adjusted parity rate	2.3/3.1	2.4/3.2
Reproductivity success rate (%)	84	82

Table 3 Fetal outcome in primary Sjögren's syndrome

	Fetal outcome/Pregnancies (%)	
	Patients with primary Sjögren's syndrome	Controls
Viable infants	111/132 (84)	117/143 (82)
Fetal wastage	21/132 (16)	26/143 (18)
Spontaneous abortions	18/132 (14)	22/143 (15)
Stillbirths	3/132 (2)	4/143 (3)
Induced abortions	75/207 (36)*	35/178 (20)
Total fetal loss	96/207 (46)	61/178 (34)
Premature infants	2/132 (2)	3/143 (2)
Caesarean sections	2/132 (2)	5/143 (3)

*p < 0.0005

Figure 1 The reported frequency of intercourse (times per week) in patients and controls was similar.

Twenty nine of 49 pSS patients were complaining of dyspareunia, eight of 20 (40%) were premenopausal while 17 of 29 (58.6%) were postmenopausal. Of the eight premenopausal patients, four had an obvious aetiology of dyspareunia (two had a perineal operation and two had vaginitis) and after appropriate treatment the dyspareunia disappeared. In the other four patients, the physical examination was normal and the cytological examination did not show signs of atrophy or inflammation. The histological examination of the vaginal mucosa in them (in two punch biopsy, in two hysterectomy after the evaluation) showed nonkeratinised stratified squamous epithelia and a mild to moderate inflammatory lymphocytic infiltration of the underlying stroma, which was more prominent around the thin-walled vessels and capillaries (fig 3).

From the postmenopausal group, one patient had scars after delivery, one had colpo-perineorrhaphy and another vulva craurosis. Of the remaining 14 patients who complained of dyspareunia, twelve also had clinical and cytological evidence of atrophic vaginitis, while the other two had a normal vagina despite the fact that they were postmenopausal for four and 21 years, respectively. An evaluation for underlying hormonal functioning neoplasia was done. The histological examination of the vaginal tissue in four of them revealed atrophic squamous epithelia. A moderately dense perivascular infiltrate of mononuclear cells, (most of which were lymphocytes) was present in the upper part of the underlying stroma (*lamina propria*). A mild stroma of fibrosis and/or oedema may also be identified (fig 4).

From the 12 patients who did not complain of dyspareunia, nine had atrophic vaginitis and the remaining three had a normal physical examination and PAP test consistent with their age.

Twenty one of the 57 women in the control group complained of dyspareunia. Only one belonged to the premenopause group (3%) and the remaining 20 to the menopause group (91%). The premenopausal woman with dyspareunia had a history of three caesarean sections. All of the post-menopausal women with dyspareunia had atrophic vaginitis cytologically confirmed. The histological picture of the vaginal mucosa in one of them was within normal limits.

While age, menopause and the sequela of these: atrophic and dry vagina seemed to affect the presence of dyspareunia in the healthy group (table 4) this was not observed in the patient group. Nevertheless, disease duration was not correlated with dyspareunia (table 4). The presence of dyspareunia was not related with any other glandular or systemic manifestation of Sjögren's syndrome except xerophthalmia ($p < 0.05$). Table 5 shows the findings from the physical examination of genitalia compared with those of the normal group in relation to their age, menopause and disease duration. No difference was observed between the two groups. Disease duration did not correlate with the presence of atrophic genitalia. Finally, no correlation was found between autoantibodies and objective, as well as subjective gynaecological findings.

Discussion

This work evaluated the obstetric and gynaecological profile of patients with primary Sjögren's syndrome. From the results, it appears that the disease does not affect the ability of these women to carry and deliver healthy babies, since fertility and parity were similar in patients and control women.

Also, the disease does not seem to negatively affect the frequency of intercourse in patients with pSS despite the coexistence of dyspareunia. Unlike controls, the age also does not appear to affect their sexual life.

In this study all patients became pregnant before the appearance of sicca symptoms, but

Figure 2 Although the intercourse frequency correlated with age ($r^2 = 0.42$) in the control group, this was not observed in the patient group ($r^2 = 0.02$).

Figure 3 Punch vaginal biopsy from a premenopausal patient with pSS showing non-keratinised stratified squamous epithelium and a mild inflammatory cell infiltration of the underlying stroma (lamina propria) [haematoxylin and eosin; $\times 160$].

this is not always the rule. In our experience, young patients with pSS have become pregnant and delivered healthy babies. However, this is not very common as the clinical picture

of the disease starts in the majority of the patients at menopause or in the fourth or fifth decade of life and after. Since the disease progresses very slowly it is generally difficult to accurately detect the date of the disease onset.¹⁴

A previous evaluation of the reproductive history of 21 pSS patients revealed a higher incidence of spontaneous abortions (21%) per woman.⁹ This was also observed in our study (data not shown), although the incidence of spontaneous abortions per pregnancy was similar to that of controls. Nevertheless, risk factors such as anticardiolipin antibodies are rarely found in pSS patients.¹⁵

It is well known that dyspareunia is common in patients with pSS.^{10, 16} In our study, 40% of our premenopausal patients had dyspareunia. Dyspareunia is painful sexual intercourse and is mainly attributed to pelvic disorders, such as vaginal dryness or vaginal infection. Vaginal lubrication is not related to the production of fluids from the local glands but is mostly a transudate through the vaginal walls and is also derived from the cervical mucous. Insufficient vaginal lubrication has usually multifactorial causes most commonly related to an oestrogen deficiency, lack of adequate sexual stimulation or both.¹⁷⁻¹⁹ An obvious cause was found in half of our patients, although in some patients with normal cytological findings dyspareunia was also reported. Despite the normal vaginal mucosa observed in premenopausal patients with dyspareunia, all patient tissues showed focal perivascular infiltrates in the dermis, a finding which was not seen in the dermis of the normal controls. In an attempt to differentiate patients with Sjögren's syndrome from a population with chronic dyspareunia, Sheeran *et al*²⁰ described a lymphocytic infiltration on the vaginal tissue from two patients who met the criteria for Sjögren's syndrome. In this report, however, the localisation of the lymphocytic infiltration is not reported. The histological picture of the vaginal tissue in all our patients with SS who underwent biopsy was clear: perivascular infiltration with chronic inflammatory cells. This lymphocytic vasculitis could be involved in the pathogenesis of dyspareunia through impaired transudate and inadequate lubrication during sexual intercourse. The number of our tissue samples from pSS patients, however, is small and thus it is quite difficult to draw definite conclusions.

The presence of this histological picture on the dermis of the vagina, however, gives a new dimension to our understanding of Sjögren's syndrome. This may be the expression of a mild vasculitic process in the genitalia. Since dyspareunia did not correlate with the systemic manifestations of the disease or vasculitis, this cannot be definitively answered. Possibly, the vaginal tissues may be affected by an inflammatory process as in other organs, such as the exocrine glands or kidney interstitium. More extensive histological studies in pSS patients with dyspareunia are required to answer these questions.

Ninety one per cent of the women at menopause in the control group had dyspareunia.

Figure 4 Punch vaginal biopsy from a menopausal patient with pSS. Note the prominent perivascular lymphocytic infiltration of the lamina propria. The covered atrophic squamous epithelium is shown on the top and the right of the field. [haematoxylin and eosin; ×250].

Table 4 Influence of different parameters on dyspareunia

	One factor ANOVA (p value)	
	Patients with primary Sjögren's syndrome	Controls
Age	0.2214	0.0001
Menopause	0.5346	0.0001
Vaginal atrophy	0.3543	0.0001
Vaginal dryness	0.0346	0.0001
Disease duration	0.6499	

Table 5 Influence of age, menopause and disease duration to the physical examination of the genital system in patients with primary Sjögren's syndrome

	One factor ANOVA (p value)		
	Age Patients with primary Sjögren's syndrome/ Controls	Menopause Patients with primary Sjögren's syndrome/ Controls	Disease duration Patients with primary Sjögren's syndrome
Atrophic clitoris	0.0719/0.0001	0.0005/0.0001	0.0394
Atrophic lips	0.0001/0.0001	0.0010/0.0001	0.0289
Atrophic vagina	0.0001/0.0001	0.0001/0.0001	0.0875
Atrophic cervix	0.0001/0.0001	0.0001/0.0001	0.0691
Atrophic uterus	0.0050/0.0001	0.0001/0.0001	0.6624
Dry vagina	0.0825/0.0001	0.0075/0.0001	0.7930
Congestive vagina	0.0105/0.0546	0.1717/0.0079	0.8516
Cervical mucus	0.0216/0.0001	0.0008/0.0002	0.6284

This probably is the result of diminished oestrogen production. In contrast, dyspareunia did not correlate with age and menopause, nor dryness of the vagina in pSS patients. Only 58% of the pSS patients at menopause complained of dyspareunia, despite the fact that their external genitalia, as well as their cytologic findings were compatible with age

changes. Furthermore, intercourse frequency in pSS patients did not decrease with age, as it was observed in the control population. These observations are difficult to interpret. Studies have indicated that patients with pSS present severe personality and psychiatric disturbances compared with age matched controls.²¹ Although this may partly explain some of our observations, the present study was not designed to address these issues. Further controlled studies which use specific instruments are needed.

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