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Authors: Magdalena A. Bizon, Aleksandra Ostrowska, Anna Wieczorek,
Włodzimierz Sawicki

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The impact of limited access of photodynamic therapy during COVID-19 pandemic on patients with vulvar lichen sclerosus

Magdalena A. Bizon¹, Aleksandra Ostrowska², Anna Wieczorek², Włodzimierz Sawicki³

¹LUX-MED Oncology Hospital, Warsaw, Poland

²Scientific Students' Group of Chair and Department of Obstetrics, Gynecology and Gynecological Oncology, Medical University of Warsaw, Poland

³Chair and Department of Obstetrics, Gynecology and Gynecological Oncology, Medical University of Warsaw, Poland

Corresponding author:

Magdalena A. Bizon

LUX-MED Oncology Hospital, sw. Wincentego 103 St., 03–291 Warsaw, Poland

e-mail: magda0504@op.pl

ABSTRACT

Objectives: Stressful situations have an impact on progression of lichen sclerosus. The aim of the study was to investigate fears and complaints of patients with vulvar lichen sclerosus and progression of disease at the beginning of the COVID-19 pandemic.

Material and methods: The analysis was based on 103 women with mean age was 64.81 ± 11.36 years divided into two groups. The first one comprised of patients with stabilization of disease during the pandemic with mean age 66.02 ± 10.01 (32–87), while the second one with progression of vulvar symptoms with mean age 63.49 ± 12.66 (25–87).

Results: Delay of diagnosis was reported to be a problem for respectively 25.93% of women from both groups. Fear about COVID-19 was described respectively by 57.4% and 55.1%. Stabilization of disease was more frequent in patients after photodynamic therapy before pandemic. Progression of vulvar symptoms and features were observed more in patients who did not conduct PDT previously. All patients from the second group who underwent photodynamic therapy reported disappointment because of no access for continuation of

treatment. On the other hand, 81.4% (43 women) regret that have no chance for trying photodynamic therapy.

Conclusions: Photodynamic therapy seems to be a method of treatment with longer survival without progression of lichen sclerosus in times of pandemics. There has been no investigation until now about concerns of patients with vulvar lichen sclerosus. Better understanding of problems connected with the pandemic can help medical personnel in taking care of patients with vulvar lichen sclerosus.

Key words: COVID-19; vulvar lichen sclerosus; fear; pandemics; photodynamic therapy

INTRODUCTION

Lichen sclerosus (LS) is one of the most frequent chronic inflammatory vulvar dermatoses with morbidity estimated as from 1:300 to as high as 1:9000. It is relatively high in women in postmenopausal age [1].

The anogenital region is affected in 85 to 98% of cases of lichen sclerosus [2, 3]. Lichen sclerosus can also affect extragenital regions, such as the chest, axillae or buttocks [4].

The most frequent symptoms are burning and itching, which cause continuous discomfort and psychological distress in many women [4–6].

The precise pathogenesis of lichen sclerosus is not known, but in 12% of patients a familial background is described [3]. The presence of autoimmune disorders often correlates with LS [7, 8]. It is believed that the development and progression of LS are closely associated with oxidative stress [9]. Excessive amounts of reactive oxygen species cause deoxyribonucleic acid (DNA) damage and peroxidation of lipids and accelerate malignant transformation. In this mechanism, smoking cigarettes induces the progression of LS. Moreover, stressful situations have an impact on progression of lichen sclerosus or promote development of new lesions of this dermatosis [9].

The most distressing aspect of these diseases is the symptoms, mainly itching and burning, disturbing everyday life and significantly reducing quality of life. Everyday usage of ointments can delay the onset of symptoms. The first line of treatment in the case of progression of this disease is glucocorticosteroid therapy [10, 11]. Lack of results after conservative treatment is an indication for induction of alternative method of treatment — photodynamic therapy with 5-aminolevulinic acid. Photosensitizer applied on the skin before the procedure is cumulated in the tissues and induce cytooxygen reactions causing death of cells. This kind of therapy causes decreasing vulvar changes [12]. Photodynamic therapy has proven to be an effective treatment in vulvar lichen sclerosus [13].

Patients with vulvar lichen sclerosis used to come to follow-up visits and routine vulvoscopy to prevent recurrence of symptoms. Vieira-Baptiste et al. reported a higher risk of progression of vulvar lichen sclerosis to vulvar cancer in the first three years after the diagnostic biopsy. However, use of ultrapotent topical steroids can reduce the risk of malignancy. Systematic gynecological visits are necessary to properly apply methods of treatment and prevent progression to vulvar cancer [14].

Halonen et al. conducted research in Finland based on 7616 women with diagnosis of vulvar lichen sclerosis in follow-up from 1970 to 2012 and confirmed that the risk of vulvar cancer was the highest in the first year of observation [15]. Extragenital lichen sclerosis does not progress to vulvar intraepithelial neoplasia (VIN) or malignant changes [16].

The coronavirus disease 2019 (COVID-19) pandemic began in December of 2019 in Wuhan. Isolation and social distancing dominated interpersonal relations and led to psychological disorders for many people. Sars-CoV2 infection induced anxiety, stress, sadness, distress, sleep disturbances and depression [17, 18]. Psychiatric disorders were more frequently diagnosed in men, while acute mental disorders were present more often in women [19]. After COVID-19 infection, more posttraumatic stress disorder (PTSD) and fear of death were observed [18, 20].

Public health organizations decided to reduce access to outpatient clinics. Also, the number of surgical procedures was limited because of the pandemic and the need for places in intensive care and anesthesiologists. Most patients with chronic diseases have no chance for follow-up. Some of the patients refused to attend follow-up visits because of fear of the pandemic. There was a group of patients who decided to apply to an outpatient clinic in the event of progression of chronic disease.

The aim of the study was to investigate fears and complaints of patients with vulvar lichen sclerosis and progression of disease at the beginning of the COVID-19 pandemic from 20th November 2020 to 28th April 2021.

MATERIAL AND METHODS

The analysis was based on 103 women with vulvar lichen sclerosis diagnosed and treated in the Outpatient Clinic of Vulvar Diseases. Every patient was treated with potent and very potent topical corticosteroids (clobetasol propionate, clobetasol dipropionate, mometasoni furoas, betametason dipropionate, hydrocortisone) in the past. About 54.4% of analyzed group (56 patients) underwent minimum one line of photodynamic therapy consists of ten courses

ended minimum three months before onset the pandemic. While COVID-19 pandemic was announced possibility of follow-up visits in Outpatient Clinic were reduced.

A cross-sectional study consisted of 20 questions was performed (Appendix 1). The first part of study concern general information of patients regarding everyday usage of emollients and rules of hygiene before pandemic. The second part gathered information about protection used by patients during the pandemic. In the third part data about the status of vulvar lichen sclerosus were collected including intensity of vulvar symptoms and new changes.

Inclusion criteria: pathological result of vulvar lichen sclerosus, visit to Outpatient Clinic of Vulvar Diseases during pandemic from 20th November 2020 to 28th April 2021, age over 18 years, no previous history of neoplasms or cancer, agreement to participate in the study.

Exclusion criteria: chemotherapy and/or radiotherapy in the past, active COVID-19 infection.

Results of the questionnaires were therefore compared with clinical examination during appointment in Outpatient Clinic. The assessment was based on objective method of visualization — vulvoscopy.

According to cross-sectional study and objective assessment during visit in Outpatient Clinic, all analyzed population was divided into two groups.

The first one comprised 49 patients with stabilization of disease during the pandemic with mean age 66.02 ± 10.01 (range 32–87) years, while the second one consisted of 54 women with progression of vulvar symptoms with mean age 63.49 ± 12.66 (range 25–87) years.

Progression of vulvar lichen sclerosus was defined as increasing intensity of vulvar symptoms and new features and progression of presented changes. Patients who had stabilization of vulvar lichen sclerosus reported no symptoms and only made routine visits to the outpatient clinic.

What is more, in the first group 91.8% of patients (45 women) were treated by photodynamic therapy. In the second group, photodynamic therapy was introduced in 20.4% (11 women). The rest of the second group did not begin photodynamic therapy because of the onset of pandemic. At the beginning of pandemic situation there was no possibility to continue photodynamic therapy because of the risk of COVID-19 infection.

Characteristics of the whole analyzed population are presented in Table 1.

Statistical methods

Means and standard deviations were used for characterization of patients. Calculation was done using Microsoft Excel (version 16.60). Statistical analysis was performed using

RStudio (version 2021.09.1). Shapiro-Wilk's test was used for normality of continuous variables. To compare continuous variables the U-Mann Whitney test was performed, to evaluate categorical variables, the chi² test was used. A p value of < 0.05 was considered significant.

RESULTS

The analysis was based on 103 women with vulvar lichen sclerosus with mean age 64.81 ± 11.36 (range 25–87) years treated in the Outpatient Clinic of Vulvar Diseases from 20th November 2020 to 28th April 2021. Results are divided according to the main points of analysis.

Fears related to visits to the outpatient clinic

Around 44.44% of the first group and 53.06% of the second group were afraid of visiting the outpatient clinic during the pandemic. Contact with medical personnel was a fear in 5.55% and 10.2% of cases. Other patients in the outpatient clinic waiting for an appointment were a reason for fear in 24.07% of the first group and 30.61% of the second group. The risk of being in quarantine was 18.52% and 12.24%.

Protective products during the pandemic

Special rules due to the pandemic situation were provided in all countries all over the world. However, all analyzed populations used different forms of protection. Percentages are presented in Figure 1.

On the other hand, 5.56% and 2.04% from both groups decided not to go outside because of the pandemic. Most patients limited their visits to town, respectively 75.93% and 67.35%. Contact only with inmates was reported by 42.6% and 30.61%, respectively. No difference between the pandemic situation and normal life was reported by 14.81% from the first group and 6.12% from the second.

Vulvar clinical symptoms during the pandemic

The first group of analyzed patients do not complain of vulvar symptoms. They use everyday ointments with no progression and observe no worsening of status, but they decided to come for a follow-up appointment.

In the second group of the analyzed population were women with progression of vulvar lichen sclerosus beginning from the onset of the pandemic. The most frequent

locations of symptoms were the ostium of the vagina (18.36%), the clitoris (12.24%), the inguinal area (6.12%), the anus (4.08%), the urethra (2.04%) and the whole vulva (2.04%).

Burning of the vulva and itching were present in most cases, respectively 28.57% and 22.45%. Reddening of the vulva was observed in 16.32% of women, while leukoplakia occurred in 6.12% and pain in 6.12%. In subgroups collected patients after photodynamic therapy in the past intensity of clinical symptoms were observed less than others.

For better assessment of intensity of syndromes, a 10-degree scale was used. All patients from the second group evaluated the intensity of every syndrome. All results are presented in Table 2.

Fears related to COVID-19 infection

Patients were asked about their fears of gynecological visits in the future. The pandemic is a situation with no end, and probably it will last for a long time. Around 29.63% of patients with no symptoms yet are afraid of progression of lichen sclerosus in the future, compared to 36.73% of the second group. Every second women from the first group are afraid of visit postponement, and 40.82% in the second group. More patients (27.78% vs 10.2%) without progression of disease were worried about transformation of the outpatient clinic to a pandemic clinic. Delay of diagnosis was reported to be a problem for 25.93% of women from the first group and 30.61% from the second one. Fears of limited access of photodynamic therapy was reported by 71.4% patients (35/49 patients), where 94.3% (33/35 patients) underwent photodynamic therapy in the past. Patients from the second group were afraid of limited access of photodynamic therapy in 83.3% (45/54 patients) including all 11 patients after photodynamic therapy in the past.

COVID-19 is a disease with various courses. This fear was described by 57.4% of women with no symptoms of lichen sclerosus and 55.1% of the group with progression of this disease. Other reported problems were lack of specialists (42.6%, 34.7%), lack of medicaments (24.07%, 16.33%), and lack of contact with family because of isolation (33.33%, 28.57%). The influence of COVID-19 on lichen sclerosus was found to be a problem for 22.22% of the first group and 16.33% of the second. All patients from the second group who underwent photodynamic therapy reported disappointment because of no access for continuation of treatment. On the other hand, 81.4% (43 women) regret that have no chance for trying photodynamic therapy.

Contact with other patients in the outpatient clinic and with inmates in correlation with fears of Sars-CoV2 infection was statistically significant in both groups in our study ($p <$

0.05). Higher risk of fear of COVID-19 infection was dependent on contact with medical personnel and other patients ($p < 0.05$). Patients are afraid of diseases and consequences of the pandemic such as quarantine or isolation. The statistical significance of correlations above are presented in Table 3.

DISCUSSION

The Sars-CoV2 pandemic causes fears and concerns of everyone all over the world. At the onset of the pandemic there were no medicaments and no possibility of vaccination, which created increasing fear, especially among patients with chronic diseases. Vulvar lichen sclerosis is a noninflammatory chronic disease, whose etiology relates to dysregulation of the immunological system. Hence, it is possible that the permanently stressful situation during the pandemic raises the risk of progression of this disease.

The pandemic situation and disturbances in taking part in routine visits cause have led to new recommendations being developed by experts [21]. During the COVID-19 pandemic vulvar cancer treatment algorithms have been modified. VIN 2 and 3 qualified for resection can be operated on with a delay of 10–12 weeks [22].

Most of the previous research estimated the risk of progression of vulvar lichen sclerosis to vulvar squamous cell carcinoma at up to 5% [23, 24].

Van de Nieuwenhof [25] analyzed 60 biopsies of vulvar lichen sclerosis and reported progression of 42% of cases to differentiated VIN and 30% with no change. Nevertheless, follow-up visits are important for monitoring progression of vulvar lichen sclerosis.

Some patients during the pandemic did not decide to attend routine visits because of fear of COVID-19 infection. Delay of these visits may be a problem in the future due to the advanced stage of cancers or intensity of symptoms with no treatment. Our study revealed the fears and concerns of patients with diagnosis of vulvar lichen sclerosis, a topic not previously reported. This group of women due to the irritating symptoms and immunological etiology of diseases is more often predisposed to exacerbating symptoms in response to a stressful situation.

The pandemic is an unexpected situation, triggering high levels of anxiety and vigilance. It is very important to study human behavior and concerns to prevent infection and prepare for everyday life [26]. Patients with lichen sclerosis suffer from various psychiatric disorders, most often anxiety (58%), depression (27%) and insomnia (19%) [9]. Moreover, due to cosmetic changes in the vulvar area, lichen sclerosis leads to a decrease in libido [27]. In China populations of adolescents during the pandemic self-reported depression and anxiety

at respectively 43.7% and 37.4% [28]. Akbarpour et al. [29] confirmed that fears of COVID-19 are associated with depression, anxiety and insomnia. In our study, there was no problem of insomnia, however, anxiety and fears concerning pandemic was observed.

Due to the COVID-19 crisis the Portuguese population had the possibility to ask the government about problems connected with the pandemic. Questions from Portuguese people were sent online, by radio or newspaper. The most frequent doubts concerned how to proceed with symptoms, how long the disease takes to develop and what treatment is available. The use of masks and gloves was often asked about. People were interested in isolation requirements and preventive behaviors. The frequency of questions was higher at the start of the study. After three weeks, the number of unknown areas gradually decreased. However, there was observed an increasing number of concerns about fake news and contradictory information regarding the pandemic [30]. In our study, patients with lichen sclerosus are afraid of contact with medical personnel and other patients. However, some of them did not use any kind of protection. On the other hand, there are also patients who do not go outside because of the pandemic.

A correlation of the COVID-19 pandemic with intensity of symptoms of vulvar lichen sclerosus has not been previously described. However, there were some cases of complications after Sars-CoV2 vaccination.

A few cases of post-vaccination vulvar ulcers have been reported. Drucker et al. observed vulvar aphthous ulcer two days after Pfizer vaccination in a 14-year-old with no previous sexual relations and no medical history [30]. Asymmetric labia, fatigue, fever and pain were also detected in a 16-year-old girl vaccinated a day before [32].

Another type of lichen striatus was reported after COVID-19 vaccination in a 42-year-old woman with no history of dermatological disorders. This kind of self-limited inflammatory dermatosis was present on the right wrist, right shoulder and chest [33]. In our study, there were no vulvar features which can be associate with COVID-19 infection.

Dermatosis after COVID-19 vaccination which appeared in a 56-year-old woman was lichen planus. She complained of lesions located on the ankles, wrist and forearms, periumbilical area, and breast with axillary folds [34]. In our study we did not observe any new atypical changes of vulvar disorders, which can develop after COVID-19 infection. The analyzed population was not affected by Sars-CoV2.

No research has presented information about the intensity of symptoms in vulvar lichen sclerosus. Nevertheless, Souaid et al. reported that 10.3% of a group treated with topical steroids and topical tacrolimus because of psoriasis and atopic dermatitis infected by

Sars-CoV2 did not present severe symptoms. Neither hospitalization nor oxygen therapy was needed. No complications in these patients were observed [35].

Patients with dermatological disorders treated with methotrexate were most hospitalized due to COVID-19 infection; however, no complications were registered [36]. Interestingly, in our analyzed population steroid therapy was introduced when clinical symptoms appeared. No one was infected by COVID-19, so we have no data about interaction between glucocorticosteroid therapy and treatment of Sars-CoV2 infection. On the other hand, there was no publication about the influence of photodynamic therapy using during COVID-19 pandemic. We only observed higher risk of progression of vulvar lichen sclerosis in case of not using photodynamic therapy before. There was no possibility of this kind of treatment at the beginning of COVID-19 pandemic what influence on disappointment of patients.

All over the world during the pandemic many rules relating to hygiene were introduced. Daily facemasks use increased. It was observed that in urban populations the percentage of people using a protective facemask was higher in Europe, North America, South America and Oceania (respectively 74.5%; 82.6%; 85.5% and 67.8%) than in Asia and Africa (50.9%; 43.8%) [37]. According to our investigation, patients prefer to use disposable and cotton facemasks. There was observed definitively lower usage of facemasks with a filter and disposable gloves. According to WHO recommendations during the pandemic, hands should be washed with 3 mL of antiseptic fluid applied for 30 seconds [38]. Interestingly, in our research, 88.89% of patients with no vulvar symptoms and 79.6% from the second groups reported performing hand disinfection during the pandemic.

Martinelli et al. [39] developed a social survey about modification of practice in gynecologic oncology during the pandemic from 49 countries all over the world. There were no modifications for treatment if the patients were COVID-19 negative in the opinion of 59% of respondents. In our study, access to an ambulatory outpatient clinic was available, but some of the patients were afraid to come. Every second patient describes fears for her life connected with the consequences of COVID-19.

CONCLUSIONS

COVID-19 is a new disease with no knowledge at the onset of the pandemic. Fears, anxiety and concerns have affected everyone everyday. Lichen sclerosis is a dermatosis with progression occurring during stressful situations, such as happened during the pandemic. Previous photodynamic therapy reduces the risk of progression of vulvar lichen sclerosis in case of stressful situation like pandemic. There has been no investigation until now about

concerns of patients with vulvar lichen sclerosis. Better understanding of problems connected with the pandemic can help medical personnel in taking care of patients with vulvar lichen sclerosis.

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Conflict of interest

None.

Supplementary material

Appendix 1.

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Table 1. Characteristics of analyzed population

Chronic diseases	Group 1	Group 2
Hypertension	21.36%	28.57%
Heart arrhythmia	4.85%	2.04%
Osteoporosis	0.97%	8.16%
Irritable Bowel Syndrome	3.88%	0%
Rheumatoid arthritis	1.94%	4.08%
Unstable angina	0.97%	4.08%
Depression	1.94%	2.04%
Glaucoma	2.91%	0%

Hypercholesterolaemia	1.94%	2.04%
Smoking	9.709%	17.476%
Neoplastic diseases	Group 1	Group 2
Breast cancer	1.94%	2.04%
Endometrial cancer	0%	2.04%
Thyroid cancer	0%	2.04%
Myeloma multiplex	0%	2.04%
Lung cancer	0%	4.08%

Table 2. Characteristic of clinical symptoms of patients from group 2

Syndrome	Median value	±	Minimum value	Maximum value
Itching	5.16	3.39	6	10
Burning	4.63	3.27	5	10
Stinging	1.08	2.27	0	9
Pain	2.12	3.03	0	10
Bleeding	0.16	0.65	0	3

Table 3. Correlations of patient's fear

Correlations		p value	OR	CI _{min}	CI _{high}
Group 1 with no symptoms					
COVID-19 infection	Contact with other patients in outpatient clinic	0.00007546	27.17	3.37	1271
	Contact with medical personnel	0.0816	Inf	0.5335	Inf
	Contact only with inmates	0.0533	3.191	0.9263	11.73
	Obligatory quarantine /isolation	0.002977	16.54	1.98	784.7
	Avoiding shopping	1	0.8212	0.06334	7.846
	Limited leaving the house	0.111	3.423	0.7357	22.17
Group 2 with intense vulvar symptoms					
COVID-19 infection	Contact with other patients in outpatient clinic	0.002066	9.996	1.823	105.4
	Contact with medical personnel	0.3532	3.9	0.3489	205.5
	Contact only with inmates	0.01515	5.51	1.186	36.07

	Obligatory quarantaine /isolation	0.6707	1.885	0.2404	22.91
	Avoiding shopping	0.2372	Inf	0.3731	Inf
	Limited leaving the house	1	1.196	0.3067	Inf

	1 st group	2 nd group
Mask from cotton	44.44%	51.02%
Mask with filter	11.11%	22.45%
Disposable mask	64.81%	44.9%
Disposable gloves	24.07%	18.37%
Washing and hand disinfection	88.89%	79.60%

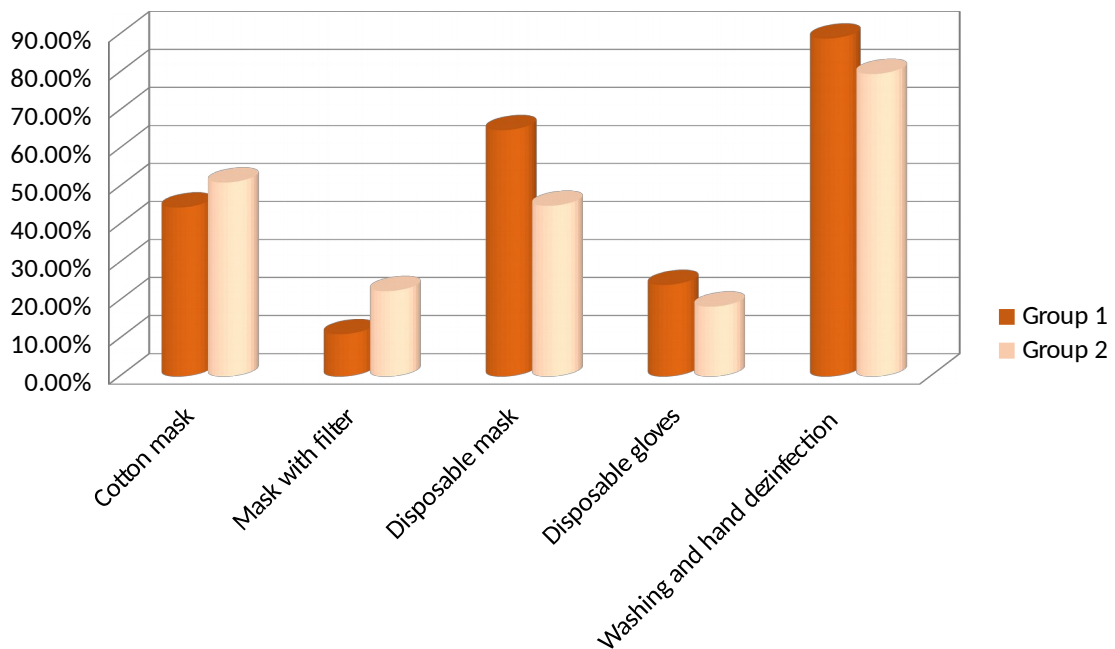


Figure 1. Usage of protective Staff by patients

Appendix 1.

Part 1. General information about patient

1. Did you attend for a gynecological visit regularly before the pandemic?
2. Are you being treated for any chronic diseases?
3. Do you smoke?
4. Which ointments do you use every day?

5. How many times a day do you use ointments?
6. Do you feel relief after daily use of ointments?
7. Do you use hygiene protective products?

Part 2. Information about symptoms

8. Have you seen new changes since the beginning of the pandemic?
9. Which location of new changes has been the most frequent since the pandemic started?
10. What was the feature of new changes on the vulva?
11. Which symptoms were the most common during the pandemic (scale 0–10)?
 - a. Itching
 - b. Burning
 - c. Stinging
 - d. Pain
 - e. Bleeding
12. Which part of the day was the most often associated with clinical symptoms?
13. Did itching cause scratching?
14. Do you often have vaginal discharge?
15. What were you afraid of during a visit to the Outpatient Clinic at the beginning of the pandemic?
16. Which protective items do you use during a visit to the Outpatient Clinic?
17. What were you afraid of during a visit to the Outpatient Clinic at the beginning of the pandemic?
18. What would you be afraid of if you were COVID-19 infected?
19. What problems did you have before a routine visit to the Outpatient Clinic at the beginning of the pandemic?
20. Which protective products do you use every day?