Presenting symptoms and diagnosis of vulvar lichen sclerosus in premenopausal women: a cross-sectional study

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Abstract

Objective: Characterize the presentation of vulvar lichen scleorsus (LS) among premenopausal women. Design: Cross-sectional study. Setting: An international web-based survey distributed on social media support groups and in two urban gynecology offices specializing in LS. Population: A total of 503 premenopausal women with biopsy-confirmed vulvar LS between the ages of 18-50. Methods: Participants completed an anonymous 28-question web-based survey between January to March 2021. Main Outcome Measures: Symptoms, timing and accuracy of diagnosis, and presence of concomitant autoimmune conditions. Results: Symptoms reported to be most present and affect the individual were dyspareunia (68%; 44%) and tearing with intercourse or vaginal insertion (63%; 39%). Symptoms that most frequently prompted patients to seek medical attention were dyspareunia (35%), pruritus (31%), and tearing with intercourse or vaginal insertion (26%). Most common skin changes included hypopigmentation (81%), vulvar fissures (72%) and labial resorption (60%), with fissures affecting the individual the most (48%). There was a 4-year delay in diagnosis with an average age of symptom onset of 27 years and average age of diagnosis of 32 years. Sixty-six percent of respondents initially received an alternative diagnosis, most commonly vulvovaginal yeast infection (49%). There is an increased incidence of hypothyroidism, vitiligo, pernicious anemia, and celiac disease. Conclusion: Premenopausal women with vulvar LS more commonly present with dyspareunia and tearing with intercourse, less often than vulvar pruritis. This condition should be considered and evaluated in women of all ages presenting with vulvar symptoms and sexual pain. Funding: None Keywords: lichen sclerosus; vulvar dermatoses; vulvar pruritis; dyspareunia

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Running Title: vulvar lichen sclerosus in premenopausal women

Abstract

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Design: Cross-sectional study.

Setting: An international web-based survey distributed on social media support groups and in two urban gynecology offices specializing in LS.

Population: A total of 503 premenopausal women with biopsy-confirmed vulvar LS between the ages of 18-50.

Methods: Participants completed an anonymous 28-question web-based survey between January to March 2021.

Main Outcome Measures: Symptoms, timing and accuracy of diagnosis, and presence of concomitant autoimmune conditions.

Results: Symptoms reported to be most present and affect the individual were dyspareunia (68%; 44%) and tearing with intercourse or vaginal insertion (63%; 39%). Symptoms that most frequently prompted patients to seek medical attention were dyspareunia (35%), pruritus (31%), and tearing with intercourse or vaginal insertion (26%). Most common skin changes included hypopigmentation (81%), vulvar fissures (72%) and labial resorption (60%), with fissures affecting the individual the most (48%). There was a 4-year delay in diagnosis with an average age of symptom onset of 27 years and average age of diagnosis of 32 years. Sixty-six percent of respondents initially received an alternative diagnosis, most commonly vulvovaginal yeast infection (49%). There is an increased incidence of hypothyroidism, vitiligo, pernicious anemia, and celiac disease.

Conclusion: Premenopausal women with vulvar LS more commonly present with dyspareunia and tearing with intercourse, less often than vulvar pruritis. This condition should be considered and evaluated in women of all ages presenting with vulvar symptoms and sexual pain.

Funding: None

Keywords: lichen sclerosus; vulvar dermatoses; vulvar pruritis; dyspareunia

Tweetable Abstract (107 characters): Premenopausal women with vulvar lichen sclerosus, an overlooked demographic, most often present with dyspareunia, not itch

Presenting symptoms and diagnosis of vulvar lichen sclerosus in premenopausal women: a cross-sectional study

INTRODUCTION

Lichen sclerosus (LS) is a chronic, inflammatory skin condition that primarily affects the anogenital epithelium in women. It has been long thought that LS presents in a bimodal distribution in premenarchal girls and postmenopausal women, largely sparing reproductive aged women. However, it has recently been reported that up to 40% of women will display cutaneous changes and onset of symptoms due to LS during their reproductive years.[1] Although LS is generally considered to be uncommon, one study conducted by practitioners experienced in vulvar dermatoses, found an incidence of one in 70 in women presenting to a general gynecologic practice, and 46% of those affected were premenopausal.[2]

Premenarchal girls may present with symptoms including pruritus, dysuria, constipation, vulvar pain, and bleeding.[3,4]Similarly, the most common presenting symptom in postmenopausal women is severe pruritis, often accompanied by dyspareunia and bleeding.[5-7] Reviews have found that less than 10% of children and adolescents are asymptomatic in presentation.[3,6] In a cohort of women with LS that included 46% premenopausal women, 39% of women were asymptomatic in the setting of advanced disease.[2]

Clinically, specialists in LS have observed that women of reproductive age often present with tearing and skin changes, rather than itch, as their primary symptoms. Vulvar pruritis is often described in conditions associated with low estrogen, such as genitourinary syndrome of menopause. A study of reproductive age women with "early onset" LS indicated that the use of androgenic oral contraceptive pills was associated with symptoms and diagnosis of vulvar LS.[8]It is possible that decreased clarity in the presenting symptoms of vulvar LS, specifically in estrogenized women, may contribute to the known five-year delay in diagnosis of this condition.[9,10]

There is a paucity of literature on presenting symptoms of vulvar LS specific to premenopausal women. Women of reproductive age may have different presenting symptoms than premenarchal girls or postmenopausal women. The purpose of this web-based observational study is to characterize the presentation of vulvar LS among premenopausal women.

METHODS

This cross-sectional study of LS among reproductive age women was approved by the George Washington University Institutional Review Board (#NCR202909). The study involved a 28-question online survey that was developed by two board-certified Obstetrician Gynecologists specializing in vulvar dermatoses. The questionnaire included Yes/No, multiple answer, and free-text responses. Demographic data included age, ethnicity, and level of education. Questions characterized symptoms experienced, which symptoms prompted medical attention, and which symptoms affected the participant the most. Information regarding time between symptom onset and diagnosis, alternative diagnoses, and additional autoimmune conditions was collected. The questionnaire was written in English.

The link to the secure survey was distributed on social media though four closed private Facebook support groups for LS. These groups have 1800, 4500, 3900, and 13,000 international members, respectively. It was also shared on women's sexual health pages on Instagram, as well as the Reddit subthread r/lichensclerosus with over 1300 members. In addition, the survey was shared with patients at two gynecology offices that specialize in vulvar conditions in Washington, D.C.. Survey data were collected over a period of seven weeks from January 9th 2021 through March 1st 2021 and managed using the secure web application Research Electronic Data Capture (RED-Cap) hosted at Children's National Medical Center (Washington, D.C.).

Inclusion criteria were a diagnosis of vulvar LS confirmed with vulvar biopsy and age of 18-50 at the time of the study. Participants over the age of 50, those reporting menopausal status, or those stating not to have had a vulvar biopsy or a vulvar biopsy inconsistent with LS were excluded from data analysis.

Numerical data were expressed as mean +/- standard deviation. Bivariate Pearson correlation was used to

determine the relationship between age of symptom onset and time interval to diagnosis. The prevalence of other autoimmune diseases within the general population were collected as reported by recent review articles in the literature.[11-17] When comparing prevalence of autoimmune diseases to the prevalence reported in our survey population, a Chi-Square test was used to analyze statistical significance. The values $P < 0.05$ were considered statistically significant.

RESULTS

A total of 956 responses to the survey were received. Of these responses, 910 met inclusion criteria for age and premenopausal status and 46 were excluded for age >50 years. A total of 503 respondents who met initial inclusion criteria reported a biopsy-confirmed diagnosis of LS (Figure 1).

The demographics are shown in Table 1, with 87% white, 4% Latina or Hispanic, 2% Asian, and 1% black. The mean age of the population was 37 years, with a range from 19-50 years (Table 1). Of those who provided specific information about symptom onset and diagnosis, the average age of symptom onset was 27 years (range 0-47 years) and average age of diagnosis was 32 years (range 2-50 years) . The population reported a mean duration of symptom onset to diagnosis of four years (range 0-37 years). Notably, 43% of individuals reported experiencing symptoms as a child (Table 2). There is an inverse correlation between the age at which symptoms began and the time interval to diagnosis with a Pearson correlation coefficient of -0.487 (t (455)=14.184,p <.0001; Figure 2).

The most prevalent symptoms among this population were dyspareunia (68%), tearing with intercourse or insertion (63%), and decreased clitoral sensation (35%). Dyspareunia (44%) and tearing with intercourse or vaginal insertion (39%) were noted to affect respondents the most. Symptoms that most frequently prompted patients to seek medical attention were dyspareunia (35%), pruritus (31%), and tearing with intercourse or vaginal insertion (26%) (Table 3; Figure 3).

In regard to vulvar skin changes, respondents endorsed hypopigmentation (81%) and the architectural changes of labial resorption (60%) and vulvar fissures (72%) most commonly. Although fissures (39%) and hypopigmentation (31%) most frequently prompted individuals to seek medical evaluation, fissures reportedly affected individuals the most (48%) (Table 4; Figure 4).

Notably, 5% of the population reported they did not seek medical attention. Rather, their diagnosis was an incidental finding upon routine pelvic examination. Sixty-six percent of respondents received an alternate diagnosis for their genital symptoms before their biopsy proven diagnosis of LS, with 49% being diagnosed with a vulvovaginal yeast infection. Other alternative diagnoses included bacterial vaginosis (23%), overactive pelvic floor dysfunction (6%), genital HSV infection (4%), atopic dermatitis (3%), estrogen deficiency (3%), vitiligo (2%), genital psoriasis (2%), lichen simplex chronicus (2%), lichen planus (1%), and scleroderma (0.2%) (Table 5).

There was an increased incidence of hypothyroidism of 10.1% among individuals with LS, significantly increased from that of the general population which is 2.0% ($X^2(1, N=503) = 29.336$, $p <0.0001$). There was also an increased incidence of vitiligo (2.6% vs 1.0%,$X^2(1, N=503) = 12.755$, $p =0.0004$), pernicious anemia (0.6% vs 0.1%,$X^2(1, N=503) = 12.408$, $p =0.0004$), and celiac disease (2.8% vs 1.4%,$X^2(1, N=503) = 6.97$, $p =0.008$) in those with LS with respect to the general population (Table 6).

DISCUSSION

Main Findings

This cross-sectional web-based study characterized the presenting symptoms of over 500 premenopausal women with biopsy-confirmed vulvar LS. Most prevalent and bothersome symptoms in premenopausal women were dyspareunia and tearing with vaginal insertion, which were more commonly reported than vulvar itch. Two-thirds of respondents were initially misdiagnosed, most commonly with vulvovaginal yeast infection, leading to an average 4-year delay in diagnosis. There is an increased incidence of hypothyroidism, vitiligo, pernicious anemia, and celiac disease with vulvar LS in this population.

Strengths and Limitations

There are inherent limitations in an observational web-based study relying on survey data and self-report. However, this study was able to recruit a large cohort of premenopausal women with vulvar LS. In order to increase accuracy in diagnosis, only respondents with biopsy-confirmed LS were included in the current analysis. Respondents were from all over the world, although the location of the participants was not recorded. Due to the low prevalence of vulvar LS in the general population, it would be difficult to collect this type of cohort through individual medical practices. Of note, non-white ethnicities where not well represented in this sample, with less than 1% of respondents identifying as black. In general, black ethnicities tend to be under-represented in web-based surveys.[18] In the literature, LS seems more common in white ethnicities; however, this may be due to reporting bias in epidemiologic studies.[19]

Interpretation

LS is historically known to have a bimodal distribution, affecting premenarchial girls and postmenopausal women, and largely sparing those of reproductive age.[20] However, this study recruited 956 premenopausal respondents with vulvar LS, approximately half with biopsy-confirmed disease and the other half with clinical disease alone. This not only confirms that LS does indeed affect females of all ages, but also that rates in reproductive-aged women may be higher than initially thought. In the literature, up to 40% of women with LS noted onset of symptoms prior to menopause.[1,10] In a gynecology practice with providers specializing in LS, 46% of the cohort identified with LS during routine gynecologic examination were premenopausal, and 39% of those patients were asymptomatic at the time of diagnosis.[2] This raises the question if the bimodal peak incidence is actually detection bias in diagnosis.[9]

Vulvar pruritis is the most commonly cited and widely described presenting symptom in vulvar LS,[20-22] noted to be present in 98% of women with biopsy-proven LS (average age 54) in one study.[22] However, most of the literature describing vulvar LS includes predominantly postmenopausal women.[6,10,21-24] In the current study, the most prevalent symptoms in premenopausal women were related to sexual function and pain, including dyspareunia, tearing with intercourse or vaginal insertion, and decreased clitoral sensation. Sexual pain symptoms were not only most commonly reported, but also most bothersome and prompted medical attention. Interestingly, decreased clitoral sensation was not reported to be bothersome or prompt medical attention. However, vulvar pruritis did prompt medical attention, even though it was not one of the most common symptoms.

In the present study, vulvar fissures were noted to be a common skin change that both affected the individual the most and prompted medical evaluation. Because vulvar pruritis is a well-known and accepted symptom of vaginitis and vulvar fissures can be associated with vulvar yeast, it is not surprising that 66% of respondents received an alternate diagnosis, half of which were misdiagnosed with vulvovaginal yeast infection and over a quarter with bacterial vaginosis. The current study found an average delay in diagnosis of 4 years. This is consistent with previous research, with a mean delay of diagnosis of 4.6 years in a cohort of girls and women of all ages with vulvar LS ranging from 1-86 years.[10] Misdiagnosis and delay in diagnosis may reflect insufficient training in identifying vulvar dermatoses. A recent survey of gynecology trainees indicated that they do not feel adequately trained in vulvar disease, including anogenital LS.[25]

Five percent of respondents reported that their condition was found incidentally on gynecologic examination. Studies report a 9% rate of asymptomatic LS as an incidental finding, but this is in all ages.[19] Goldstein et al. reported that 39% of asymptomatic women (46% premenopausal) were diagnosed with vulvar LS incidentally on routine gynecologic examination by practitioners skilled in diagnosing vulvar dermatoses.[2] In the present study, participants were recruited from social media groups focusing on the condition. It is likely that those women who are asymptomatic would be less likely to be present in these groups and less likely to engage in the study, possibly accounting for a lower rate of asymptomatic disease at diagnosis in this cohort.

Although decreased levels of estrogen and testosterone have not been shown to cause lichen sclerosus, it is possible that reproductive hormones may play a role in symptomatology. Gunthert et al. conducted a

retrospective cohort study comparing 40 premenopausal women with vulvar LS compared to 100 controls with no vulvar skin condition. The authors noted all of the women with LS were using oral contraceptive pills, compared to 66% use in the control group. Specifically, they found that use of anti-androgenic birth control pills was associated with a 2.5 increased risk of early onset LS. The authors concluded that anti-androgenic birth control pills could be a cause involved in LS.[8] However, the most recent data favors autoimmune and genetic etiologies for anogential LS.[26] It is possible that those with LS have a genetic predisposition, thus decreasing estrogen and androgen levels "uncover" or worsen symptoms of vulvar LS, namely vulvar pruritis. This would explain why vulvar LS may be more symptomatic when estrogen levels are low prior to puberty, seem to improve or disappear in many women during the reproductive years, but then become more prevalent in menopause, when estrogen levels decline.

Supporting an autoimmune etiology, it is known that LS is associated with other autoimmune conditions. The current study found an increased incidence of hypothyroidism, vitiligo, pernicious anemia, and celiac disease compared to population data. There was a 10% rate of hypothyroidism in the study population, compared to a reported rate of autoimmune thyroiditis of 12-15% in two previously studied cohorts.[27,28] These studies included women of all ages. Incidence of thyroid disease increases with age, which supports a slightly lower rate found in our study population. Although celiac disease is not commonly cited as an associated autoimmune condition with LS, there has been a recent case report describing anogenital LS in three premenarchal girls with celiac disease[29] and one report of a 53 year-old women with extragenital LS and celiac disease.[30] Although this has not been explored in the literature, many patients with vulvar LS find that a gluten-free diet improves their symptoms. More research is necessary to determine if there is an association between celiac disease or gluten sensitivity and vulvar LS and how diet can affect LS symptomatology.

CONCLUSION

Although previous studies have included women of reproductive age, samples are typically skewed in the postmenopausal range, which adds caution in generalizing data on symptom presentation and diagnosis to younger women. Based on current findings, it is necessary to screen women of all ages who present with sexual pain and tearing at the introitus for vulvar LS. When first-line treatments for vulvovaginal yeast infection are not effective and skin changes of the vulva are present, LS should be considered, especially in premenopausal women.

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Disclosure of Interests:

Jill Krapf: Dr. Krapf is a consultant for Mahana Therapeutics and Good Clean Love.

Andrew Goldstein: Dr. Goldstein is President of the Gynecologic Cancer Research Foundation, a 501 c3 non-profit corporation, which provided partial funding for this study. He is a part-time employee of Dare Bioscience. He has received research funding from Dare Science, SST, Endoceutics, The Cellular Medicine Association, and Ipsen. He is a consultant for Ipsen, SST, and AMAG

Alyssa Smith: no disclosures

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Contribution to Authorship

JMK: conception, planning, carrying out, analyzing, writing up of the work; AS: planning, analyzing, writing up of the work; SC: planning, carrying out, analyzing, writing up of the work: AG: conception, planning, carrying out, writing up of the work.

Details of Ethical Approval: This study was approved by The George Washington University Institutional Review Board, #NCR202909.

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Table/Figure Captions

Figure 1: Flow chart of participant inclusion and exclusion criteria.

Figure 2: Time to diagnosed by age of symptom onset.

Figure 3: Number of participants reporting symptoms of decreased clitoral sensation, dyspareunia, tearing with intercourse or vaginal insertion, pruritis, and soreness/pain/tenderness based upon symptoms experienced, symptoms promoting medical evaluation, and symptoms that affected the individual the most.

Figure 4: Number of participants reporting vulvar architectural or pigment changes of hypopigmentation, labial resorption, clitoral phimosis, vulvar fissures, and vaginal stenosis based upon symptoms experienced, symptoms promoting medical evaluation, and symptoms that affected the individual the most.

Table 1: Demographics of the study population, including age, ethnicity, and education.

Table 2: Age at symptom onset and time to diagnosis. *non-numerical responses were excluded.

There is an inverse correlation between the age at which symptoms began and the time interval to diagnosis with a Pearson correlation coefficient of -0.487 (t (455)=14.184, p <.0001.

Table 3: Symptoms experienced, symptoms prompting medical evaluation, and symptoms that affected the individual most

Table 4: Architectural or pigmentation changes experienced, prompting medical evaluation, and those that affected the individual most

Table 5: Patient-reported initial alternative diagnoses for their genital symptoms.

Table 6: Patient-reported coexisting autoimmune disorders diagnosed and prevalence of these disorders in the general population based upon reported literature.

Table 1. Demographics of the study population, including age, ethnicity, and education

N=503	
Age	Mean (St. Dev)
	37 (8)
Ethnicity	n (%)

White/Caucasian	437 (86.9)
Black/African-American	4 (0.8)
Latina or Hispanic	22 (4.4)
Asian	9 (1.8)
Native American	0 (0)
Native Hawaiian or Pacific Islander	0 (0)
Two or more	15 (3.0)
Other/Unknown	14 (2.8)
Prefer not to say	2 (0.4)
Education	n (%)
Some High School	7 (1.4)
High School	93 (18.5)
Bachelor's Degree	230 (45.7)
Master's Degree	114 (22.7)
Doctorate or higher	19 (3.8)
Trade School	28 (5.6)
Prefer not to say	12 (2.4)

Table 2. Age at symptom onset and time to diagnosis.

N = 457*	
	Mean (St. Dev)
Age of symptom onset	27 (11)
Age of diagnosis	32 (10)
Time from onset of symptoms to diagnosis (N=457)	4 (6)
	n (%)
Symptoms present as a child	215 (43)

Table 3. Symptoms experienced, prompting medical evaluation, and those that affected the individual most

N = 503 **Symptom**	N = 503 **Experienced** n (%)	N = 503 **Prompting evaluation** n (%)	N = 503 **Affected individual most** n (%)
Decreased clitoral sensation	177 (35)	19 (4)	63 (13)
Dyspareunia	342 (68)	174 (35)	223 (44)
Tearing with intercourse or insertion	319 (63)	133 (26)	196 (39)
Pruritus	82 (16)	157 (31)	124 (25)
Soreness/Pain/Tenderness	17 (3)	29 (6)	25 (5)

Table 4. Architectural or pigmentation changes experienced, prompting medical evaluation, and those that affected the individual most

N = 503 **Architectural or pigmentation change**	N = 503 **Experienced** n (%)	N = 503 **Prompting evaluation** n (%)	N = 503 **Affected individual most** n (%)
Hypopigmentation	409 (81)	158 (31)	82 (16)
Labial resorption	304 (60)	35 (7)	89 (18)

Clitoral phimosis	196 (39)	31 (6)	68 (14)
Vulvar fissures	364 (72)	195 (39)	242 (48)
Vaginal stenosis	188 (37)	43 (9)	62 (12)

Table 5. Alternate diagnoses for genital symptoms

N = 503	N = 503
Diagnosis	n (%)
None	172 (34)
Yeast infection	245 (49)
BV infection	113 (23)
Genital HSV infection	19 (4)
Vitiligo	11 (2)
Genital psoriasis	12 (2)
Atopic dermatitis	16 (3)
Lichen planus	7 (1)
Lichen simplex chronicus	9 (2)
Scleroderma	1 (0.2)
Pelvic floor dysfunction	32 (6)
Estrogen deficiency	13 (3)

Table 6. Coexistent autoimmune disorders

N = 503			
Autoimmune disorder	n (%)	General prevalence, %	P value
Hypothyroidism	51 (10.1)	2.0	7.6×10^{-39}
Hyperthyroidism	2 (0.4)	1.3	0.07
Alopecia areata	14 (2.8)	1.7	0.06
Vitiligo	13 (2.6)	1.0	0.0004
Pernicious anemia	3 (0.6)	0.1	0.0004
Celiac	14 (2.8)	1.4	0.008
Lichen planus	7 (1.4)	1.0	0.39
Psoriasis	13 (2.6)	1.6	0.08

Figure 1

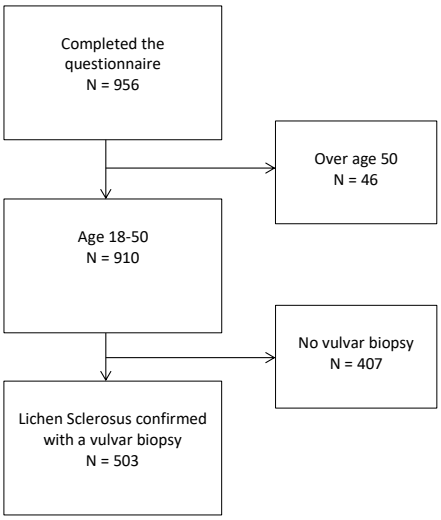

Figure 2. Time to diagnosis by age of symptom onset