A LONGITUDINAL MULTI-INSTITUTIONAL STUDY OF VULVAR LICHEN SCLEROSUS: FROM CHILDHOOD TO PERIMENOPAUSE

Running title: Vulvar lichen sclerosus before menopause

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Précis: premenarchal age group demonstrate significantly higher rates of subepithelial hemorrhage, fissuring, blistering, and open sores.

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ABSTRACT

Objective: The main outcome of this study was the evaluation of clinical characteristics, comorbidities, and therapeutic approaches in patients with Vulvar Lichen Sclerosus (VLS) aged from childhood to perimenopause. Secondly, it was intended to compare these characteristics according to the menarchal status.

Methods: Patients less than 45 years of age with a diagnosis of VLS from January 2002 to June 2022 in 10 referral centers, were included in this retrospective longitudinal study. The univariate analysis compared the dependent variables according to menarchal status.

Results: 186 patients met the inclusion criteria. At diagnosis, between 25 and 40% of pre-menarchal patients reported signs related to sub-epithelial hemorrhage. A significantly greater presence of bleeding ($p<0.005$), easy bruising ($p=0.028$), fissures ($p=0.008$), petechiae/splinter hemorrhages ($p<0.001$), and bleeding/blistering or open sores ($p=0.011$) was observed in premenarchal patients respect to postmenarchal group. The perineum ($p =0.013$) and the perianal region ($p <0.001$) were significantly more involved in the premenarchal group. Topical calcineurin inhibitors were more used in the premenarchal population ($p=0.003$), while Vitamin E oil and moisturizers were more used in the postmenarchal population ($p=0.047$).

Conclusions: VLS is a chronic condition that can cause vulvar changes that result in severe morbidity and affects sexual function and quality of life, even before menopause. VLS continues to be misdiagnosed in this population. This may lead to an average delay from symptom onset to diagnosis. Evaluating clinical manifestations of VLS in pre-menarchal and post-menarchal age allowed us to find different clinical characteristics between the two periods suggestive of the diagnosis.

KEYWORDS: vulvar lichen sclerosus; premenopause; childhood; perimenopause; menarche; vulvar cancer.

INTRODUCTION

Vulvar Lichen Sclerosus (VLS) is a chronic dermatological condition that predominantly affects the anogenital region, resulting in a significant impact on quality of life. The etiology is unclear: studies have shown an association with autoimmune conditions, atopy, genetic susceptibility, and genital infections[1]. Onset is bimodal, typically before puberty or after menopause[2]. The first peak of incidence accounts for 7–15% of all VLS cases[3]. It is estimated that VLS occurs in 1:900 of premenarchal girls. These prevalence data may be underestimated because clinical signs and symptoms at onset may be non-specific[4].

While several studies have investigated VLS in different populations, specific considerations for premenopausal women remain relatively scarce. However, recent research has highlighted the unique challenges and implications of VLS in this demographic. Krapf JM et al.[5] shed some light on VLS in premenopausal populations (18-50 years), but there is a notable gap in the focus on juvenile age, a distinct subgroup dealing with their unique physiological and hormonal milieu.

The most common presenting symptoms in children, such as vulvar pruritus, discomfort, dysuria, and constipation are non-specific for diagnosis[6]. A small percentage of patients may be asymptomatic, and the gynecologist may be naturally reluctant to perform a biopsy in the pediatric patient. For these reasons, VLS continues to be misdiagnosed in this population, who are often treated with antifungals and oral antibiotics before a proper diagnosis is made. This can lead to an average delay from symptom onset to diagnosis of 1.3 years[7].

Studies on the effect of menarche on the disease are emerging[8], but studies reporting specific clinical characteristics of young patients with VLS are scarce in the literature.

A careful study of this category of patients could provide the clinician with more information to recognize this rare pathology from childhood to menopause and to establish the correct treatment as soon as possible.

This research aims to build on existing studies and comprehensively investigate VLS from childhood to perimenopausal women, examining the different clinical nuances of VLS in these patients. Specifically, the present study aimed to assess any information on clinical characteristics (signs, symptoms, architectural changes), comorbidity, and therapeutic approaches in patients less than 45 years of age. Secondly, it was intended to compare the clinical characteristics of patients according to menarchal status.

MATERIALS AND METHODS

This retrospective longitudinal multi-institutional study included women treated at 10 Italian referral centers, between January 2002 and June 2022, with a follow-up of at least 12 months. The study

design provides that the procedures and data of interest had already been performed or gained according to routine clinical practice before starting the study. All data were abstracted from the medical records and recorded on a special case report form (CRF). After checking that the same patient had not been seen in two different centres, a unique progressive number was assigned to each subject to anonymise personal data. According to the Italian law on non-interventional observational studies[9], patient consent was not an essential requirement, and the Ethics Committee took note of the study (file 2023/18).

All patients included had to have a first clinical or histopathological diagnosis of VLS before of 45 years. This age limit was chosen because it precedes the second peak of VLS incidence[2] and precedes the median age of the early menopausal transition[10], according to the Stages of Reproductive Aging Workshop (STRAW) criteria,[11] to reduce the bias related to this phase of hormonal changes. All patients in post-menopausal status (even if under the age of 45) at the time of their initial diagnosis were excluded. For secondary outcomes, patients were divided into two subgroups: pre-menarchal and post-menarchal, according to their status at symptom onset. For each patient the following data were collected: age, age of menarche, age at diagnosis, age at symptoms onset and months of delay in diagnosis, clinical features considered as present or absent (*symptoms* like itching, dysuria, burning, bleeding, enuresis or incontinence, abdominal pain, superficial and deep dyspareunia, and *signs* like atrophic skin on labia majora, atrophic skin on labia minora, smooth discolored skin patches, blotchy wrinkled skin patches, easy bruising, fragile skin, bleeding/blistering or open sores, urethra stenosis, introital stenosis, hyperkeratosis, hypochromia with 8 morphology, fissures, petechiae/splinter hemorrhages), site of involvement (labia majora, labia minora, clitoris, urethra, perineum, perianal), presence of comorbidities (diabetes, hypertension, dyslipidemia, major adverse cardiovascular event [MACE], neurological or psychiatric symptoms, thyroiditis and others Immune Mediated Inflammatory Diseases [IMID], use of alcohol, smoking habit), previous or ongoing treatments (topical corticosteroids**,** topical calcineurin inhibitors [TCI], imiquimod, laser therapy, methotrexate, topical retinoids, photodynamic therapy, phototherapy, topical Vitamin E and moisturizers, avocado and soybean unsaponifiable [ASU]). The mode of use of the therapy was defined as *proactive* or *reactive*, as described by Makowska et al[12]. Follow-up report forms recording clinical data from regular clinic visits were analysed. The incidence of vulvar intraepithelial neoplasia (VIN) and/or vulvar squamous cell carcinoma (VSCC) was also recorded.

Statistical analysis

Categorical variables were expressed as numbers and percentages. Continuous variables were tested using the Kolmogorov–Smirnov test and expressed as median and range or mean and standard

deviation according to distribution. Qualitative variables were expressed as numbers and percentages. For secondary analysis, the univariate analysis compared dependent variables according to menarchal status. Continuous variables were compared using the Student's *t*-test. The non-parametric Mann-Whitney U-test for two independent samples was used for values that were not normally distributed. The chi-squared test or the Fisher's exact test were used to compare categorical variables.

MedCalc Statistical Software was used to perform statistical analyses (MedCalc® Statistical Software, Ostend, Belgium, version 20.218; https://www.medcalc.org, accessed 1 April 2023). A value of $p \leq 0.05$ was considered statistically significant (two-tailed analysis).

RESULTS

One hundred eighty-six patients who met the inclusion and exclusion criteria were included, with a mean age of 32.4 ± 11.65 (range: 5-45 years), and a median follow-up of 12 months (range: 6-120 months). The median delay from symptom onset to diagnosis was 7 months (range: 0-240 months). The dropout rate during follow-up was of 19.9% at 6 months, 39.2% at 12 months, 54% at 24 months, 77.42% at 36 months, 82.8% at 48 months, 86.6% at 60 months, and 93.5% at 120 months.

Table 1 shows the baseline characteristics of the patients and the comparison between the pre-menarchal and post-menarchal populations. Thyroiditis or other IMID was present in 24.1 % of patients. A histopathological diagnosis of VLS was made in approximately 45% of patients. The median age of women who underwent biopsy was 38 years (range: 9-45). The rate of histological diagnosis was significantly higher in postmenarchal women ($p<0.001$).

The clinical characteristics of the study population at diagnosis and the comparison between the pre-menarchal and post-menarchal groups according to their status at the time of symptom onset are shown in **Table 2.** At the time of diagnosis, between 25 and 40 per cent of pre-menarchal patients reported signs related to susceptibility to skin bleeding and the formation of subepithelial hemorrhage. Pre-menarchal patients reported a significantly higher incidence of skin bleeding (21.7% vs. 2.5%, $p=0.002$), easy bruising (30.4% vs. 12.9%, $p=0.028$), fissures (39.1% vs. 16%, $p=0.008$), petechiae/splinter hemorrhages (30.4% vs. 3.1%, $p<0.001$), and bleeding/blistering or open sores (26.1% vs. 8.6%, $p=0.011$) compared to the post-menarchal group. Six months after diagnosis, the following signs and symptoms remained significantly different: bleeding (10.5% vs. 0%, $p<0.001$), constipation (12.5% vs. 0.8%, $p=0.002$), easy bruising (21% vs. 6.1%, $p=0.025$), and blistering or open sores (21% vs. 1.5%, $p<0.001$). At the 12-month follow-up, premenarchal patients were more likely to have blistering or open sores (25% vs. 1 %, $p<0.001$), fragile skin (31.3% vs. 11.2%, $p=0.032$), or fissures (18.8% vs. 4.1%, $p=0.024$). At the same follow-up, post-menarchal patients had a significantly higher prevalence of atrophic skin on the labia minora (52% vs. 18.8%, $p=0.014$). At

diagnosis, the perineum and the perianal region were significantly more involved in the pre-menarchal group (39.1% vs. 17.1%, p =0.013 and 39.1% vs. 11.4.1%, p <0.001, respectively). A significantly higher rate of perianal involvement in pre-menarchal patients persisted at 6 and 12 months from diagnosis (21% vs. 6.9%, p =0.004, and 31.3% vs. 4.1%, p <0.001, respectively). In patients of post-menarchal age, significantly greater involvement of of the labia minora (70.8% vs. 47.4%, p =0.04, and 76.5% vs. 37.5%, p =0.001, respectively), and of the clitoris (66.9% vs. 21%, p <0.001, and 54.1% vs. 18.8%, p =0.009, respectively) was observed at 6 and 12 months follow-up.

Table 3 shows the therapeutic approaches used in the study population, and the comparison between the pre-menarchal and post-menarchal groups. Prior to diagnosis, approximately one third of the patients had already received high-potency corticosteroid therapy, and TCIs were used significantly more in the pre-menarchal population, whereas vitamin E oil and moisturisers were used more in the post-menarchal population. No significant differences in therapeutic approaches were observed at diagnosis and 6-month follow-up. At 12-month follow-up, high-potency topical corticosteroids were used significantly more in the post-menarchal group (60.6% vs. 31.3%, p = 0.029), while TCIs were used more in the pre-menarchal population (18.8% vs. 2%, p = 0.002).

Data on clinical status at 6-month follow-up are available for 80.1% of patients: 102 patients (68.8%) showed clinical remission or improvement of signs or symptoms, 40 (26.9%) showed unchanged symptoms or signs, and 7 (4.7%) showed clinical worsening. Proactive therapy was used in 65% of patients (66/102), while reactive therapy was used in 35% of cases (36/102). At the first follow-up, a higher number of patients in the post-menarchal group showed significant clinical improvement or remission of signs and symptoms of VLS compared to the pre-menarchal population (64.6% vs. 36.8%, p=0.02). At 12 months, follow-up data are available for 60.8% of patients: 55/113 patients (48.7%) had clinical remission or improvement of signs or symptoms, 46/113 patients (40.7%) had unchanged symptoms or signs, and 12/113 (10.6%) had clinical worsening. Proactive therapy was used in 76.6% of patients (59/77), while reactive therapy was used in 23.4% of cases (18/77). At 6-month and 12-month follow-up, a higher rate of post-menarchal patients received proactive therapy compared to the other group (55.7% vs. 17.6%, p = 0.003, and 60.2% vs. 20%, p = 0.004, respectively), while there were no differences in the rate of patients receiving reactive therapy.

The clinical status of disease worsening did not reveal any independent risk factors associated with this occurrence (type of therapy prescribed at diagnosis, clinical features, site of involvement, family history of VLS or other autoimmune diseases). In particular, there were no significant differences between patients with aggravation and those with no change, remission or improvement in symptoms or signs. No cases of VSCC were found during follow-up. One case of differentiated VIN was reported.

DISCUSSION

At present, the literature on VLS focuses predominantly on postmenopausal women, with few studies focusing specifically on premenopausal women. However, recent evidence suggests that VLS may have different characteristics in this population and that specific research is needed[5].

Krapf et al.[5], in 2022, in a web-based population study of women aged between 18 and 50 years, reported a 4-year delay in diagnosis of VLS. However, they only included biopsy-confirmed diagnoses, which may increase this delay. Our mean delay to diagnosis was only 7 months. This may be explained by the fact that our study involved referral centers with gynecologists and dermatologists dedicated to the juvenile population. The same authors reported that the predominant symptom was dyspareunia (68%) and, less frequently, pruritus (31%)[5]. In our study, restricting the analysis to the sexually active population, we found a rate of superficial and deep dyspareunia of 30% and 16%, respectively. The rate of pruritus in our patients is around 80% at diagnosis, but significantly lower (52%) in the premenarchal group.

Premenarchal VLS can present with a variety of symptoms including pruritus, dysuria, constipation, vulvar pain, and bleeding[13,14]. While symptoms such as pruritus are completely non-specific, skin bleeding and constipation are most suggestive of the diagnosis of VLS in our pre-menarchal group, in accordance with what was reported by Winfrey OK et al. in 2022[15]. We found that some of the signs that favoured the diagnosis of VLS in premenarchal age were significantly associated with subepithelial haemorrhage. Borghi et al. reported that dermoscopy of VLS revealed irregular linear vessels in over 97% and dotted vessels in almost 45% of early stages VLS[16]. Before menarche, thinning of the subcutaneous tissue, and the presence of atrophic skin may make these signs more apparent. Bleeding, ecchymoses, and hemorrhagic lesions must not only raise the suspicion of sexual abuse but must add the differential diagnosis of this specific dermatosis. Furthermore, the significantly greater involvement of the clitoris in the post-menarcheal age[15] found by Wynfrey OK et al. is confirmed in our population. It is rare in childhood, when the development of the external genitalia must be completed.

On physical examination, post-menopausal VLS most commonly affects clitoral hood, labia minora, inner part of labia majora, perineum and perianal region sometimes resembling “figure of eight,” with involvement of the vulvar and perianal regions[1,17]; the characteristic findings are ivory-white skin, erosion, hyperkeratosis, atrophy, and disturbance of vulvar architecture like labial resorption,

adherence of opposing labia, covering of the clitoris and narrowed vestibule of the vagina[17]. While these signs are easily recognized in women over the age of 50, in our population, the signs associated with atrophy, hyperkeratosis, and hypochromia showed a lower prevalence (overall between 9% and 17%, with the presence of atrophic skin on the labia minora alone in about 40% at the time of diagnosis). Restricting the analysis to our premenarchal population, it showed a significantly higher rate of perineal and perianal involvement compared to the post-menarchal population, which showed more anterior vulvar involvement. This reaffirms the need to pay particular attention to the gynaecological examination of children, where perianal involvement may be the only finding, associated with constipation due to painful fissures in this area, as reported by Orszulak D[6]. The significantly lower use of histopathological diagnosis in the infant population of our study is understandable, probably to reduce invasive diagnoses that may cause local pain.

The aims of treatment include relieving symptoms and preventing or minimising scarring. There are no randomised controlled trials evaluating treatments in premenopausal women. The mainstay of treatment is high-potency topical corticosteroids, as is the case in postmenopausal women. TCIs are a reasonable choice for short-term second-line therapy[18], according to the European guidelines for the treatment of VLS[19], which emphasise that 0.03% tacrolimus ointment is an effective and safe form of VLS therapy. Li et al. conducted a study in 14 girls aged 4–11 years[20] and found only 22% relapse at 12-months follow-up in the girls who received maintenance treatment with tacrolimus ointment twice a week for six months, concluding that TCI appears to be an effective and safe therapy in the treatment of VLS in children. Similar results were obtained by Mazzilli et al, who conducted a study in 10 girls aged 4-9 years[21] and found a significant improvement in pruritus, pain and constipation with no relevant side effects. Given the high prevalence of bleeding/blistering or open sores, fissures, and signs of subepithelial haemorrhage in premenarchal age, which can be exacerbated by high-potency steroids, TCI may be an alternative option, especially after remission of symptoms. In our study, TCI were used significantly more in the premenarchal population, probably because most of these patients were seen by expert and experienced paediatric dermatologists. The use of TCIs is closely related to the immune-mediated pathogenesis of VLS, which is known to be often associated with other autoimmune diseases, such as thyroiditis, present in approximately 15% of cases in our population, in line with what has been reported in two previous cohort studies[22-23]. Surgery is reserved for complications such as functional impairment24. No patients in our population underwent surgery. Some symptoms may resolve spontaneously after menarche; the course of the disease can be latent, but omplete resolution occurs in only a minority of girls[8,15]. Furthermore, up to 75% of patients with permanent architectural changes persist into adulthood[8].

Limitations of our study include the inability to document the evolution of VLS in relation to menarche, the retrospective nature of the study, and the high dropout rate during follow-up. The very high dropout rate may have affected the outcome statistics, particularly 1) response to therapy, 2) clinical remission, and 3) risk of developing malignancy. A similar high rate of dropout rate was reported in a large series[25]. It is probably difficult to persuade young women to undergo prolonged follow-up after symptom control for a disease that has a very low risk of developing cancer before menopause. However, a major advantage of our study is the large number of people with premenopausal VLS, which allows us to describe the signs and symptoms of this group of patients.

The absolute risk of VSCC in young women is very low, regardless of VLS, and is probably unknown due to the lack of long-term follow-up data. The lifetime risk of VSCC in women with inadequately treated or untreated VLS is estimated to be 2-5%[25,26] compared with approximately 0.3% in the general female population. Treatment appears to reduce the risk. We did not observe any cases of neoplastic disease of the vulva in our population, but such a short median follow-up does not allow us to draw any conclusions.

In young women, other therapies may also be an option for quality of life improvement. If alternative or additional therapies are used, biopsy may be considered to confirm the diagnosis before starting treatment[27]. Preliminary data suggest that autologous fat grafting[28] and fractional microablative CO2 laser[29] may improve symptoms and quality of life in these patients. These data need to be confirmed in adequately powered randomised controlled trials.

CONCLUSIONS

Evaluating the clinical manifestations of VLS before and after menopause allowed us to identify different characteristics between the two periods. Knowing more about the typical characteristics of the disease before menopause may be crucial in facilitating clinical diagnosis and minimising diagnostic delay, which can lead to serious morbidity and sequelae.

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ABBREVIATIONS

Vulvar Lichen Sclerosus (VLS)

Case Report Form (CRF)

Stages of Reproductive Aging Workshop (STRAW)

Major Adverse Cardiovascular Event [MACE]

Immune Mediated Inflammatory Diseases [IMID]

Topical Calcineurin Inhibitors [TCI]

Avocado and Soybean Unsaponifiable [ASU]

Vulvar Intraepithelial Neoplasia (VIN)

Vulvar Squamous Cell Carcinoma (VSCC)

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