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# EMAS clinical guide: Vulvar lichen sclerosus in peri and postmenopausal women

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#### ABSTRACT

*Introduction:* Vulvar lichen sclerosus (LS) is a chronic inflammatory disease which affects genital labial, perineal and perianal areas, producing significant discomfort and psychological distress. However there may be diagnostic delay because of late presentation and lack of recognition of symptoms.

Aims: The purpose of this clinical guide is to provide advice on early recognition and treatment. *Material and methods:* Literature review and consensus of expert opinion.

Results and conclusions: The etiology of LS in peri and postmenopausal women is unknown, although autoimmune, genetic and infectious factors have been implicated. Definitive diagnosis of non-malignant disorders depends on the histology of biopsied tissue. LS associated with cellular atypia should be classified as intraepithelial neoplasia. Topical corticosteroids are the most effective treatment, although prolonged treatment may be associated with dermal atrophy. Topical calcineurin inhibitors, such as tacrolimus or pimecrolimus, may be a safe and effective alternative treatment without risk of corticosteroid-related vulvar atrophy since they do not affect collagen synthesis. LS recurrences are frequent, and can lead to significant physical discomfort and emotional distress that affect mood and sexual relationships. Anatomical changes may require surgical management.

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# 1. Introduction

Lichen sclerosous (LS) is a chronic progressive, non-neoplastic, epithelial atrophic disease with a marked inflammation that manifests as patchy, thinner than normal white fibrous skin. It affects more women than men, and may be found in different sites, although the most common is in the external genitalia (85–95% of cases) [1–3]. Vulvar LS has also been called lichen albus, hypoplastic dystrophy, and vulvar kraurosis. The predominant symptoms are pruritus and pain, although many women have a long asymptomatic period. Women with LS have an increased risk of squamous

cell carcinoma, and human papillomavirus infection or radiothe-

of onset: prepubertal girls and peri- or postmenopausal women [3]. Some scientific organizations have issued consensus guidelines about vulvar skin disorders and/or LS management [4–6]. The purpose of this clinical guide is to provide advice on early recognition and treatment in peri- and postmenopausal women.

## 2. Prevalence

While LS is a common condition, its prevalence is uncertain [3,7,8]: calculated incidences range between 1:300 and 1:1000 new patients referred to a general hospital. In general gynecological practice the rate of histologically proven LS is about 1.7% [7,9], and 54% are postmenopausal (mean age 52.6 years) and 39%

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rapy may be involved in carcinogenesis.

Vulvar LS can occur at any age but tends to have two peaks

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are asymptomatic [7]. The prevalence of LS is probably underestimated since a third of cases are asymptomatic [7]. There can also be delays in seeking medical advice and a range of specialists consulted who may be unfamiliar with the condition. Common misdiagnoses includes *Candida albicans* vulvitis and postmenopausal atrophy and leading to delays of in diagnosis of up to 5 years [10].

## 3. Etiology

The etiology of LS remains unknown, but several mechanisms have been studied and suggest a multifactorial origin, including a genetic, auto-immune, and infectious background. Genetic predisposition to LS has been shown in family and twin studies [11,12]. Sherman et al. studied 1052 women with LS (80% histologically confirmed) using family clustering, and reported that 126 (12%) women had a positive family history of the condition [13].

There is a strong association between LS and autoimmune disease [14,15] in adults. LS-associated immune system disorders include scleroderma, Hashimoto thyroiditis, rheumatoid arthritis, psoriasis, and alopecia areata [9,14,16]. In a series of 211 patients with confirmed LS, 29.9% had thyroid disease and this was not age-dependent and higher than that reported in the general population [17].

Genital LS may coexist with morphea or local scleroderma and with systemic sclerosis. In a series of 472 patients with local scleroderma LS was more frequent as indicated by an odds ratio of 18.1 [16]. A possible association between LS and psoriasis has also been reported [9,18]. Thus, the prevalence of psoriasis in LS women (7.5%) is higher than in the general population. Oral lichen planus (LP) and vulvar LS may coexist. However, prevalence of oral LP in women with vulvar lichen sclerosus (0.6%) is similar to that reported for oral LP in the general population (1–2%) [19].

Women with LS may have other bladder, bowel and pain comorbidities. Thus in a series of 308 women with LS seen at a vulvar clinic, self-reported conditions were overactive bladder 15.3%, stress urinary incontinence 27.9%, constipation 32.5%, irritable bowel syndrome 19.5%, thyroid dysfunction 33.1%, fibromyalgia 9.1%, temporomandibular joint disorder 13.0% and vulvar pain 83.1% [20].

Infection, such as with *Borrelia burgdorferi* (BB), has been implicated but the evidence is contradictory [21,22]. The Koebner phenomenon, which is described as the occurrence of lesions at sites of injured or traumatized skin, is a well-known manifestation of LS. Thus repeated trauma and irritation to the area may actually be precipitating factors to the expression of this disease [23].

# 4. Clinical characteristics

Careful history taking and clinical examination are important [23]. Vulvar LS most commonly presents with progressive pruritus, dyspareunia, dysuria, or genital bleeding. It usually affects the ano-vulvar epithelium, although in 20% of patients other areas are involved such as the upper trunk, axillae, buttocks and lateral thigh. It does not affect the vagina and cervix. Initially the vulva is itchy, sore, bright and red. Hemorrhagic bullae may be also present in the genital area, which can be confused with other vulvar ulcerative disease.

After several years, the vulva becomes ivory with atrophic changes leading to loss of labia minora, burying of the clitoris, obstruction of urinary outflow, reduction of the vaginal introitus and fourchette adhesions. Chronic scratching secondary to pruritus can result in subepithelial hemorrhaging. Perianal involvement can create the classic "figure of eight" shape. Constipation and painful defecation may be a feature. LS can have a negative effect on sexual function, including dyspareunia, apareunia and difficulty to reach

orgasm. Assessment should also include investigation for autoimmune disease.

## 5. Histopathological diagnosis

Although LS can be diagnosed on clinical examination, histological confirmation should be sought. Biopsy should be performed of hyperkeratotoic areas, erosions that do not improve with treatment or sites with altered pigmentation.

Differential diagnosis could include LP, vitiligo, immunobullous disorders such as cicatricial pemphigoid, and vulvar intraepithelial neoplasia (VIN). Squamous cell hyperplasia (SCH), which increases the risk of vulvar malignancy, may be present in acanthotic areas. Patients with lichen sclerosus have an increased risk of developing squamous cell carcinoma. Women with LS associated vulvar cancer are significantly older than women with LS alone, and SCH is independently associated with vulvar carcinoma. The duration of symptoms and loss of vulvar architecture are indicators of cancer risk [4].

#### 6. Treatment

As there is no cure for LS, the endpoints of treatments are symptoms relief and improvement of anatomical changes. Treatments may be pharmacological or surgical, but there are few randomized trials [24,25]. Ultra-potent topical corticosteroid creams such as clobetasol propionate are the treatment of choice [5,24], with topical calcineurin inhibitors second line [6,26]. Once LS is controlled, maintenance treatment is based on the use of corticosteroids or moisturizers [27,28]. Psychosexual counseling should be discussed and offered as LS can affect sexual function [5]. Vaginal dilators may be helpful. It is generally advised to avoid bubble baths, scented soap, detergents, perfumes, etc. as these may irritate the vulva but the evidence base for this is scant.

## 6.1. Local corticosteroids

Clobetasol propionate cream (0.05%) significantly reduces symptoms and improves skin characteristics compared with placebo [24]. A recommended regimen for a newly diagnosed case is clobetasol propionate 0.05% ointment applied once daily, at night, for 4 weeks, then on alternate nights for 4 weeks, and then twice weekly for a further 4 weeks, before review. About 60% of patients experience complete remission of their symptoms. Others will continue to have flares and remissions; they are advised to use clobetasol propionate 0.05% as required [5].

The less potent steroid mometasone furoate (0.1% cream) is also effective [5,29]. Triamcinolone ointment has also been reported to reduce LS symptoms in a small study [30]. Intralesional injection of triamcinolone acetonide has been proposed as an alternative treatment to topical treatment of LS, but again the studies are small [31].

Pruritic LS has also been treated with topical corticosteroids or combined corticosteroid and monthly anesthetic/corticosteroid subdermal injection. In this 5-year study, time to recurrence was longer with the combined treatment, although women were less satisfied with the injections [32].

The side effects of topical corticosteroids include irritation, burning, dryness, hypopigmentation, and dermal atrophy.

#### 6.2. Calcineurin inhibitors

Calcineurin inhibitors (CIs) are immunomodulators that block the release of inflammatory cytokines from T lymphocytes. Topical tacrolimus and pimecrolimus have been reported to be associated with good clinical response in anogenital LS [5]. However studies have involved a small number of patients [26,33–36]. Use is recommended in women with corticosteroid-resistant disease or intolerance to these compounds. The long-term safety profile of these compounds is not established and there are concerns about the increased risk of neoplasia [5].

## 6.3. Topical androgens and progesterone

Testosterone propionate cream (2%), dihydrotestosterone cream (2%) and progesterone cream have been compared with placebo treatment in randomized controlled trials [24]. Two of these studies used testosterone for 3 months and one year, respectively, without significant differences as compared with placebo. A very small randomized placebo-controlled trial of dihydrotestosterone for 3 months found no significant improvement. Similarly topical progesterone was of no benefit.

## 6.4. Surgical management

Surgical management of LS such as vulvectomy or cryosurgery is reserved for women with malignancy or postinflammatory sequelae [5,38]. As studies are limited, there is a need to increase the evidence base.

#### 6.5. Other treatments

### 6.5.1. Other pharmacologic treatments

Retinoids may reduce hyperkeratinisation and have antiinflammatory properties. Topical tretinoin (0.025%) has been used in a small group of women with histologically proven LS. Symptoms, macroscopic and histological characteristics significantly improved after 4–13 months [5,37,38]. As retinoids are teratogenic, they are contra-indicated in pregnancy; they may also be associated with local skin reactions [39].

The antihistaminic and anti-inflammatory compound oxatamide has topically studied in a placebo-control comparative study in vulvar LS. It seems that oxatamide had a better anti-itching effect than placebo but not on other clinical endpoints [40].

Since an infectious etiology has been implicated in vulvar LS, antibiotics have been studied but the numbers of patients have been small. An observational study of 15 women, who had previously responded poorly to topical corticosteroids, tested the use of penicillin or cephalosporins. Rapid relief of pain, pruritus and burning was noted [41].

# 6.5.2. Photodynamic therapy

An open study of photodynamic therapy (PDT) (topical 5-aminolaevulinic acid with argon laser light) found that 10 out of 12 patients had significant improvement [42]. Another study demonstrated good symptomatic benefit in 6 of 10 patients treated with aminolaevulinic acid PDT using a bioadhesive patch [43].

## 7. Follow-up and prognosis

There is no consensus with respect to the follow-up of women with vulvar LS [4]. The risk of malignancy in uncomplicated female genital LS that has been diagnosed and treated is small being less than 5% [5,4]. After initial diagnosis and treatment, follow-up at 3 and 6 months to assess response is recommended. If women continue to use a topical steroid annual follow-up would be prudent. Long-term follow-up in specialist clinics rather than primary care is appropriate for women with troublesome symptoms, localized skin thickening, previous cancer or VIN. Women should be encouraged to examine their vulva for any changes though this may be

difficult in older women with co morbidities such as osteoarthritis, visual problems and obesity. In women with both estrogen deficient urogenital atrophy and LS, treatment for both conditions can be concurrent, but there are no randomized controlled trials. In this setting low dose vaginal estrogens [44] could be used along with vulvar corticosteroids.

#### 8. Recommendations

- Women presenting with vulvar pruritus and pain should be examined by a health professional with expertise in vulvar skin disorders
- Diagnosis may need to be confirmed by biopsy, particularly in those cases that do not respond to corticosteroid treatment, to exclude VIN or vulvar cancer.
- First line treatment is topical clobetasol propionate cream (0.05%) and calcineurin inhibitors (tacrolimus or pimecrolimus) are second line.
- Surgical management such as vulvectomy or cryosurgery is reserved for women with malignancy or post-inflammatory sequelae.
- While women should be encouraged to examine their vulva for any changes this may be difficult or impossible in the elderly with co-morbidities, hence careful inspection of the external and internal genitalia is recommended during every gynecologic consultation, particularly in postmenopausal women.

#### **Contributors**

FRPL prepared the initial draft which was circulated to all EMAS board members for comment and approval, production was coordinated by MR and FRPL.

# **Competing interests**

None declared.

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## Provenance and peer review

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## References

- Ridley CM, Neill SM. Non-infective cutaneous conditions of the vulva. In: Ridley CM, Neill SM, editors. The vulva. Oxford: Blackwell Science; 1999. p. 121.
- [2] Thomas RH, Ridley CM, McGibbon DH, Black MM. Anogenital lichen sclerosus in women. Journal of the Royal Society of Medicine 1996;89:694–8.
- [3] McPherson T, Cooper S. Vulval lichen sclerosus and lichen planus. Dermatologic Therapy 2010;23:523–32.
- [4] Jones RW, Scurry J, Neill S, MacLean AB. Guidelines for the follow-up of women with vulvar lichen sclerosus in specialist clinics. American Journal of Obstetrics and Gynecology 2008;198:496e1–3.
- [5] Neill S, Lewis FM, Tatnall FM, et al. British Association of Dermatologists' guidelines for the management of lichen sclerosus 2010. British Journal of Dermatology 2010;163:672–82.
- [6] Royal College of Obstetricians and Gynaecologists. The management of vulval skin disorders. Green-top Guideline 58; February 2011 http://www.rcog.org.uk/files/rcog-corp/GTG58Vulval22022011.pdf [accessed 13.11.12].
- [7] Goldstein AT, Marinoff SC, Christopher K, Srodon M. Prevalence of vulvar lichen sclerosus in a general gynecology practice. Journal of Reproductive Medicine 2005;50:477–80.
- [8] Leibovitz A, Kaplun VV, Saposhnicov N, Habot B. Vulvovaginal examinations in elderly nursing home women residents. Archives of Gerontology and Geriatrics 2000;31:1–4.

- [9] Eberz B, Berghold A, Regauer S. High prevalence of concomitant anogenital lichen sclerosus and extragenital psoriasis in adult women. Obstetrics and Gynecology 2008;111:1143–7.
- [10] Cooper SM, Gao XH, Powell JJ, Wojnarowska F. Does treatment of vulvar lichen sclerosus influence its prognosis? Archives of Dermatology 2004;140:702–6.
- [11] Meyrick Thomas RH, Kennedy CT. The development of lichen sclerosus et atrophicus in monozygotic twin girls. British Journal of Dermatology 1986;114:377-9.
- [12] Cox NH, Mitchell JN, Morley WN. Lichen sclerosus et atrophicus in non-identical female twins. British Journal of Dermatology 1986;115;743.
- [13] Sherman V, McPherson T, Baldo M, Salim A, Gao XH, Wojnarowska F. The high rate of familial lichen sclerosus suggests a genetic contribution: an observational cohort study. Journal of the European Academy of Dermatology and Venereology 2010;24:1031–4.
- [14] Cooper SM, Ali I, Baldo M, Wojnarowska F. The association of lichen sclerosus and erosive lichen planus of the vulva with autoimmune disease: a case–control study. Archives of Dermatology 2008;144:1432–5.
- [15] Kazandi M, Sahin C, Terek MC, Cirpan T, Oztekin K. Clinical evaluation of vulvar lichen sclerosus: case series. European Journal of Gynaecological Oncology 2010;31:555–8.
- [16] Kreuter A, Wischnewski J, Terras S, Altmeyer P, Stücker M, Gambichler T. Coexistence of lichen sclerosus and morphea: a retrospective analysis of 472 patients with localized scleroderma from a German tertiary referral center. Journal of the American Academy of Dermatology 2012;67:1157–62.
- [17] Birenbaum DL, Young RC. High prevalence of thyroid disease in patients with lichen sclerosus. Journal of Reproductive Medicine 2007;52:28–30.
- [18] Simpkin S, Oakley A. Clinical review of 202 patients with vulval lichen sclerosus: a possible association with psoriasis. Australasian Journal of Dermatology 2007;48:28–31.
- [19] Saunders H, Buchanan JA, Cooper S, Hollowood K, Sherman V, Wojnarowska F. The period prevalence of oral lichen planus in a cohort of patients with vulvar lichen sclerosus. Journal of the European Academy of Dermatology and Venereology 2010;24:18–21.
- [20] Berger MB, Damico NJ, Menees SB, Fenner DE, Haefner HK. Rates of self-reported urinary, gastrointestinal, and pain comorbidities in women with vulvar lichen sclerosus. Journal of Lower Genital Tract Disease 2012;16:285–9.
- [21] Eisendle K, Grabner T, Kutzner H, Zelger B. Possible role of Borrelia burgdorferi sensu lato infection in lichen sclerosus. Archives of Dermatology 2008;144:591–8.
- [22] Zollinger T, Mertz KD, Schmid M, Schmitt A, Pfaltz M, Kempf W. Borrelia in granuloma annulare, morphea and lichen sclerosus: a PCR-based study and review of the literature, Journal of Cutaneous Pathology 2010;37:571–7.
- [23] Funaro D. Lichen sclerosus: a review and practical approach. Dermatologic Therapy 2004;17:28–37.
- [24] Chi CC, Kirtschig G, Baldo M, Brackenbury F, Lewis F, Wojnarowska F. Topical interventions for genital lichen sclerosus. Cochrane Database of Systematic Reviews 2011;(12):CD008240.
- [25] Abramov Y, Elchalal U, Abramov D, Goldfarb A, Schenker JG. Surgical treatment of vulvar lichen sclerosus: a review. Obstetrical and Gynecological Survey 1996;51:193–9.
- [26] Goldstein AT, Creasey A, Pfau R, Phillips D, Burrows LJ. A double-blind, randomized controlled trial of clobetasol versus pimecrolimus in patients with vulvar lichen sclerosus. Journal of the American Academy of Dermatology 2011;64:e99–104.
- [27] Bradford J, Fischer G. Long-term management of vulval lichen sclerosus in adult women. Australian and New Zealand Journal of Obstetrics and Gynaecology 2010;50:148–52.

- [28] Simonart T, Lahaye M, Simonart JM. Vulvar lichen sclerosus: effect of maintenance treatment with a moisturizer on the course of the disease. Menopause 2008:15:74-7.
- [29] Cattaneo A, De Magnis A, Botti E, Sonni L, Carli P, Taddei GL. Topical mometasone furoate for vulvar lichen sclerosus. Journal of Reproductive Medicine 2003;48:444–8.
- [30] LeFevre C, Hoffstetter S, Meyer S, Gavard J. Management of lichen sclerosus with triamcinolone ointment: effectiveness in reduction of patient symptom scores. Journal of Lower Genital Tract Disease 2011;15: 205-9.
- [31] Stücker M, Grape J, Bechara FG, Hoffmann K, Altmeyer P. The outcome after cryosurgery and intralesional steroid injection in vulvar lichen sclerosus corresponds to preoperative histopathological findings. Dermatology 2005:210:218-22.
- [32] Ventolini G, Swenson KM, Galloway ML. Lichen sclerosus: a 5-year follow-up after topical, subdermal, or combined therapy. Journal of Lower Genital Tract Disease 2012;16:271–4.
- [33] Luesley DM, Downey GP. Topical tacrolimus in the management of lichen sclerosus. British Journal of Obstetrics and Gynaecology: An International Journal of Obstetrics and Gynaecology 2006;113:832–4.
- [34] Kim GW, Park HJ, Kim HS, et al. Topical tacrolimus ointment for the treatment of lichen sclerosus, comparing genital and extragenital involvement. Journal of Dermatology 2012;39:145–50.
- [35] Hengge UR, Krause W, Hofmann H, et al. Multicentre, phase II trial on the safety and efficacy of topical tacrolimus ointment for the treatment of lichen sclerosus. British Journal of Dermatology 2006;155: 1021–8
- [36] Kauppila S, Kotila V, Knuuti E, Väre PO, Vittaniemi P, Nissi R. The effect of topical pimecrolimus on inflammatory infiltrate in vulvar lichen sclerosus. American Journal of Obstetrics and Gynecology 2010;202: 181e1-4.
- [37] Bradford J, Fischer G. Surgical division of labial adhesions in vulvar lichen sclerosus and lichen planus. Journal of Lower Genital Tract Disease 2013;17(January):28–32.
- [38] Virgili A, Corazza M, Bianchi A, Mollica G, Califano A. Open study of topical 0.025% tretinoin in the treatment of vulvar lichen sclerosus. One year of therapy. Journal of Reproductive Medicine 1995;40:614–8.
- [39] British National Formulary. http://www.medicinescomplete.com/mc/bnf/ current/PHP7822-topical-retinoids-and-related-preparations-for-acne.htm [accessed 01.12.12].
- [40] Origoni M, Ferrari D, Rossi M, Gandini F, Sideri M, Ferrari A. Topical oxatomide: an alternative approach for the treatment of vulvar lichen sclerosus. International Journal of Gynaecology and Obstetrics 1996;55: 259-64
- [41] Shelley WB, Shelley ED, Amurao CV. Treatment of lichen sclerosus with antibiotics. International Journal of Dermatology 2006;45:1104–6.
- [42] Hillemanns P, Untch M, Pröve F, Baumgartner R, Hillemanns M, Korell M. Photodynamic therapy of vulvar lichen sclerosus with 5-aminolevulinic acid. Obstetrics and Gynecology 1999;93:71–4.
- [43] Zawislak AA, McCluggage WG, Donnelly RF, et al. Response of vulval lichen sclerosus and squamous hyperplasia to photodynamic treatment using sustained topical delivery of aminolevulinic acid from a novel bioadhesive patch system. Photodermatology, Photoimmunology and Photomedicine 2009;25: 111-3
- [44] Rees M, Pérez-López FR, Ceasu I, et al. EMAS clinical guide: low-dose vaginal estrogens for postmenopausal vaginal atrophy. Maturitas 2012;73: 171-4.