Diagnosis and Treatment of Vulvar Lichen Sclerosus: An Update for Dermatologists

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REVIEW ARTICLE

Diagnosis and Treatment of Vulvar Lichen Sclerosus: An Update for Dermatologists

Andrew Lee[1,2,3] · **Gayle Fischer**[1,2,3]

Abstract
Vulvar lichen sclerosus is an important skin disease that is common in women in their 50 s and beyond; however, it can also affect females of any age, including children. If not treated, it has the potential to cause significant and permanent scarring and deformity of the vulvar structure. In addition, if untreated, it is associated with a 2–6% lifetime risk of malignant squamous neoplasia of the vulva. Lichen sclerosus has been considered a difficult to manage condition; however, both serious complications can potentially be prevented with early intervention with topical corticosteroid, suggesting that the course of the disease can be treatment modified.

Key Points

Vulvar lichen sclerosus treated inadequately can lead to scarring and permanent deformity of the vulva.

Long-term maintenance treatment with topical corticosteroids can keep vulvar lichen sclerosus in remission and potentially reduce the risk of vulvar malignancy.

Patients with vulvar lichen sclerosus require long-term follow-up even after initial remission is achieved, with a physician who is adequately experienced in managing this condition, as it may continue to silently progress or reappear without causing symptoms.

1 Introduction

Lichen sclerosus (LS) is an uncommon and potentially serious skin disease that has a predilection for the genital skin and is much more often encountered in females than males. This makes it common in vulvar practice, responsible for at least 10% of new cases [1]. The prevalence in the whole population is essentially unknown because of under-diagnosis and referral bias. It has been reported as 1.7% of all patients in a general gynecology practice [2]. A recent study from the Netherlands estimated the incidence at 14.6 per 100,000 women years [3]. It occurs in all age groups, including children. The mean age of onset is in the mid to late 50 s, with only about one third of cases occurring in women under 50 years [2, 3]. In the pediatric group, vulvar lichen sclerosus (VLS) can occur as early as in the first few years of life. Pediatric disease accounts for 7–15% of all cases [4]. In the pediatric setting, LS almost always affects the genital area, with only approximately 6% of these patients having extragenital involvement [5]. Until recently, it was believed that pre-pubertal VLS resolved at puberty, but recent evidence has shown that this is not consistently true [6, 7].

Although LS may occur on any part of the skin, it is almost always a genital condition, involving the vulva, perineum and perianal skin. Extragenital lesions are most common on the neck, buttocks, inner thigh, shoulders and wrists (Fig. 1).

VLS is an important condition to diagnose correctly and manage actively for two reasons. First, if not treated aggressively, it may significantly scar, shrink and deform

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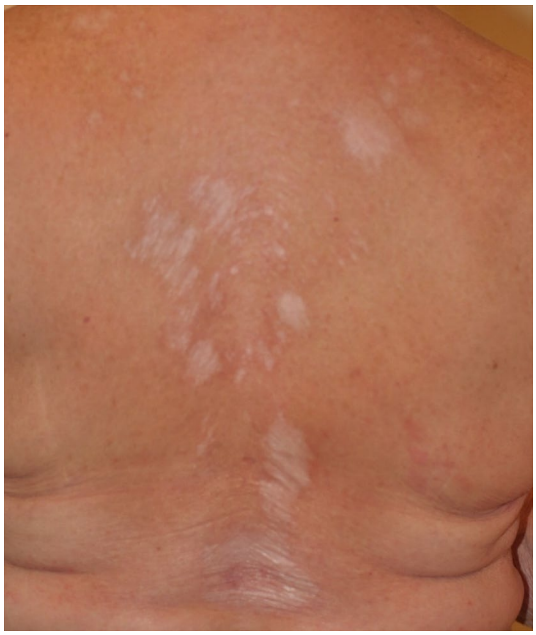

Fig. 1 Extragenital lichen sclerosus on the back

the vulva and cause stenosis of the introitus, with resulting impact on quality of life. Second, it is a risk factor for malignant squamous cell neoplasia of the vulva, including invasive squamous cell carcinoma and vulvar intraepithelial neoplasia, with the lifetime risk of untreated or inadequately treated disease being 2–6% [3, 8]. This is unusual for a skin condition. Rarely do either of these complications occur in other dermatoses, an example being cutaneous discoid lupus. However, recent research suggests that both can be prevented by early intervention, and even with later intervention, cancer and further scarring can be arrested [9]. Therefore, these patients require lifelong observation and encouragement to continue treatment. This is a fact that has been under-investigated and is therefore lacking in much of the existing literature on the subject.

2 Etiology

The true etiology of LS remains unknown. Studies have observed high rates of autoimmune disease in patients with LS and even higher levels of detection of autoantibodies, but this does not confirm that LS itself is definitely autoimmune. A confounding factor is that middle-aged female patients, the main cohort with this condition, have a relatively high rate of autoantibodies. A well conducted study found that relative to aged-matched controls, LS patients do suffer from autoimmune disease more often: about 30% as opposed to 10% in the whole population [10]. As well, about 30% had a positive family history. However, the same study found that there was no significant difference between the rate of autoantibody detection between patients with LS and controls. The two diseases seen most often in association were autoimmune thyroid disease and vitiligo.

Additionally morphoea, alopecia areata and pernicious anemia have been linked to LS [11, 12]. Diabetes, psoriasis and coeliac disease have all been reported to co-exist, but it is possible that this is coincidence [13–15]. More recently, LS has been found to have a higher incidence (17%) in patients with Turner's syndrome [16].

A study has demonstrated that 67% of patients in a cohort of 30 with LS had serum immunoglobulin G (IgG) antibodies to ECM-1 compared to 7% of controls [17]. This often quoted research unfortunately has not brought us any closer to knowing the pathogenesis; however, it does strengthen the presumption that VLS is an autoimmune condition despite the fact that this has never been confirmed.

The majority of patients with LS are otherwise well with no personal or family history of autoimmune disease. It is not uncommon to find low titer positive antinuclear antibody (ANA); however, this is rarely significant enough to warrant further investigation. Thyroid autoantibodies may also be present, and if this is the case, further investigation is warranted. Even in the presence of thyroid auto-antibodies, thyroid function may be normal [18].

LS can certainly run in families, although it is more common for it to be a chance phenomenon [19]. This has led to a search for a human leukocyte antigen (HLA) association. Although no association with the autoimmune-related HLA antigens (HLA A1, B8 and DR3) has been reported, the HLA class II antigens HLA-DQ7, HLA-DR11 and HLA-DR12 have the strongest association with susceptibility to LS [20].While these documented HLA associations are of interest, unfortunately, there is a lack of significant data to conclusively comment on the strength of these associations.

Epigenetic changes can cause functional impairment of the genome not related to DNA sequence. These changes can lead to altered gene expression and phenotypic changes. Recent research has identified altered enzyme expression in VLS resulting from an epigenetic change and pointing to a possible epigenetic background for pathogenesis [21].

3 Diagnosis and Disease Course

3.1 Clinical Presentation in Adults

The most common presenting symptom of VLS is itch (93%), often of a severe, life- and sleep-disrupting nature. There is sometimes pain as a result of excoriation or fissuring [9]. Distressing clitoral hyperesthesia may occur, and dyspareunia is very common. Other symptoms include

dysuria, sexual dysfunction and bleeding from skin fissures of the vulva and perianal skin.

VLS has a significant impact on quality of life and sexual functioning [22]. However, occasionally, VLS can be completely asymptomatic, discovered by chance by the patient or by the general practitioner during a Pap smear test. This is rare but important, as the disease may be advanced at presentation as a result. This situation can be dangerous, as asymptomatic disease may not be noticed by the patient until carcinoma arises [23].

The appearance of a well-defined white sclerotic plaque with an atrophic wrinkled surface is typical (Fig. 2). However, there are many variations. These include:

- Multiple white papules or macules producing a speckled appearance
- Thickened hyperkeratotic plaques
- Plaques limited to small areas such as the tips of the labia minora or the clitoris or clitoral hood
- Edema on a background of pallor
- Telangiectasia, purpura, hemorrhagic blistering on a background of pallor
- Angiokeratomas on a background of pallor (Fig. 3)
- Fissures and traumatic ulcers (Fig. 4)
- Erosions
- Blisters
- LS associated with vulvar psoriasis, which appears erythematous
- Brown hyperpigmentation similar to post-inflammatory hyperpigmentation which can supervene (Fig. 5).

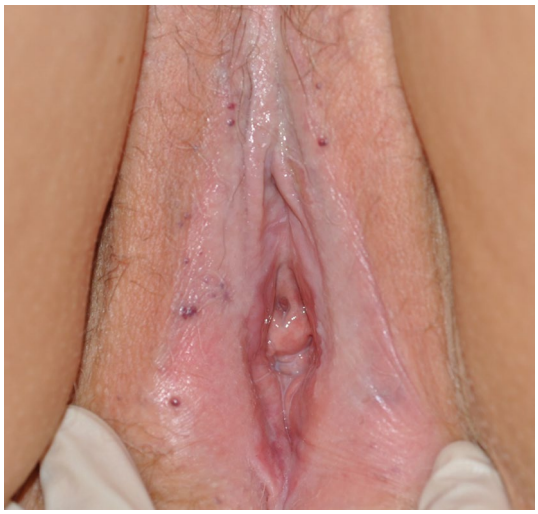

Fig. 3 Angiokeratomas on a background of pallor (lichen sclerosus)

The distribution of VLS is also very variable. The classic textbook description is of a figure of eight encircling the vulva, perineum and perianal skin. However, it can affect only the perianal region, clitoris, and internal surface of the labia majora, labia minora, and the vaginal introitus. VLS very rarely involves the vagina proper (that is, within the hymen). The exception is where squamatization of the vaginal wall has occurred as a result of prolapse [24].

A key point in recognizing VLS, particularly in the late stage, is that the vulvar shape is often not normal. While it is true that the size of the labia minora is highly variable, virtually all women develop them. If they are completely

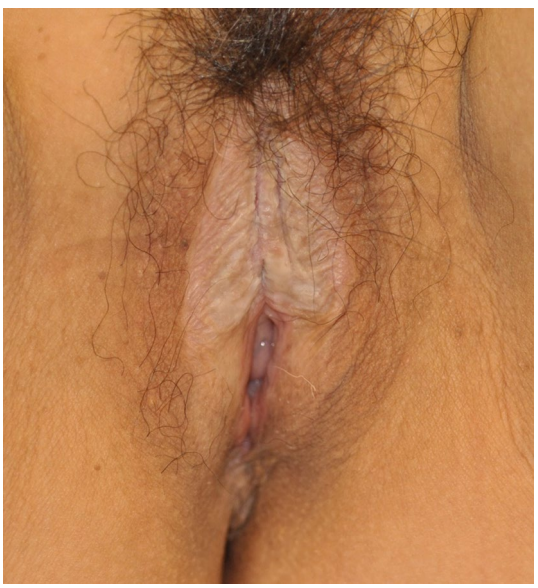

Fig. 2 Lichen sclerosus with a typical atrophic wrinkled surface

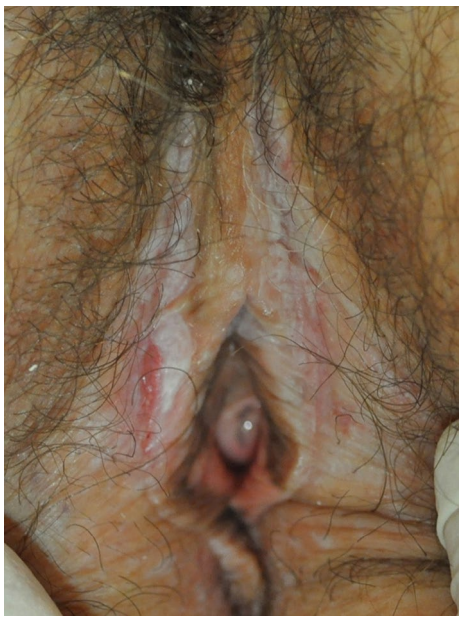

Fig. 4 Lichen sclerosus: fissures and traumatic erosions

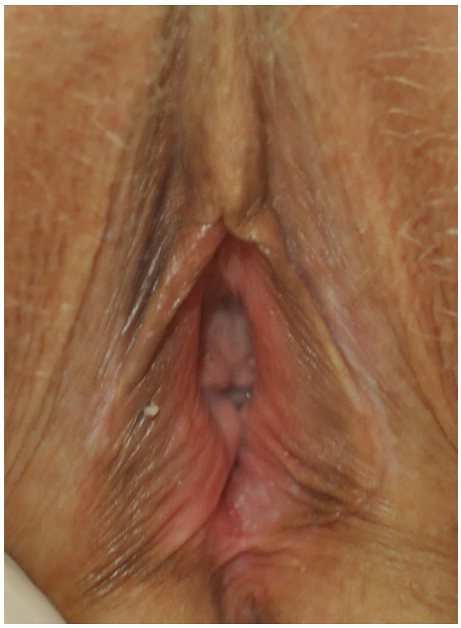

Fig. 5 Brown hyperpigmentation in lichen sclerosus, which appears similar in appearance to post-inflammatory hyperpigmentation

missing or if the clitoris has shrunk or is buried under scar tissue, this is very suggestive of this condition, and indeed the only other conditions which can result in this appearance are lichen planus, graft-versus-host disease and the very rare mucous membrane pemphigoid, all of which are erosive conditions. In some cases, VLS and lichen planus can occur concurrently in an overlap condition, with VLS of the vulvar skin and lichen planus involving the vestibule and vagina [25].

VLS obeys the Koebner phenomenon, and therefore localizes into areas of friction and trauma. This possibly explains why it is usually most recalcitrant on the perineum and the inner surfaces of the labia minora. It has also raised a question regarding the role of urinary incontinence, particularly in the setting of treatment resistance [26].

3.2 Dermoscopy

The dermoscopic appearance of VLS has recently been documented. Patchy white structureless areas, comedo-like openings, purpuric globules, scale, "ice slivers" and sparse, thin vessels are described and are changed by treatment [27].

3.3 The Course of the Disease in Adults

The course of VLS is unpredictable, but if left untreated, about half of the patients will lose structure of the vulva, with the labia minora eventually becoming reabsorbed, and the clitoris becomes entrapped and buried, revealing an overall atrophic, shiny, white vulva missing normal anatomy [9]. The timeframe over which this happens is, anecdotally, a few years, but has never been accurately estimated. It is very typical for the labia minora to fuse with the labia majora laterally and with each other subclitorally. The fusion line is brittle and easily tears during intercourse. Perineal fissuring and tearing is also common. Eventually, the vaginal opening may become significantly stenosed, with pooling of urine within the vagina, simulating urinary incontinence. Once scarring has occurred, it is in most cases irreversible. In advanced disease, gross distortion of vulvar anatomy may occur. There have not been any studies to determine which patients are prone to scarring.

Between 2 and 6% of patients with VLS will progress to malignancy [3, 28]. Which patients are prone to this is not predictable, and it is therefore necessary to regard all as at risk [29].

One study suggested that the patients with hyperkeratotic disease were most at risk for malignant change, but this may have been flawed by selection bias [30]. A more recent study found that the only differentiating factor between those who developed malignant change and those who did not was whether their disease was consistently suppressed with treatment [9].

In the past, there has been controversy regarding the possibility that the course of the disease could be modified by treatment, and this has led to a nihilistic approach that addresses only symptoms and not signs, which has been expressed in the most recent guideline [31]. However, a recent study has shown that ongoing topical corticosteroid (TCS) maintenance treatment that is matched to the severity of the disease so that it is suppressed will prevent both scarring and carcinoma [9].

Little is known of the course of the disease in pregnancy; however, recent data suggest that it is unchanged and that treatment should be continued during pregnancy, without adjustment from non-pregnant treatment. TCSs are considered safe in pregnancy. Patients with LS can usually have a normal vaginal delivery [32].

3.4 Histopathology

The definitive diagnostic test for LS is a skin biopsy, which should be taken from the most densely white area. The histopathology is distinctive and uniform across all ages. The epidermis is often atrophic with hydropic degeneration of basal cells and a homogenous pale zone of hyalinization in the upper dermis. In the dermis, there is a variable lichenoid infiltrate of mononuclear cells.

When VLS has been treated with TCS, the biopsy can become non-specific; however, in this situation, the skin usually looks normal as well [33]. If a patient presents with a presumptive diagnosis of VLS that is already treated, with both normal cutaneous appearance and biopsy, the only

clue to the presence of the disease may therefore be loss of structure.

Although VLS has a characteristic clinical appearance, a skin biopsy, taken at first presentation, from the affected site provides diagnostic confirmation and exclusion of alternate diagnoses. A positive biopsy is also helpful in counseling the patient about the important long-term consequences and the need for follow-up. It is also useful if the patient changes location or medical practitioners. Treated disease may appear normal, and some authors have called for biopsy prior to treatment whenever possible so that there is a clear, histopathological record of the diagnosis [34].

In children, a clinical diagnosis is almost always sufficient because biopsy is traumatic. The list of differential diagnoses is small, including most frequently vitiligo and lichenification, which may appear pale and is usually associated with eczema. Neoplastic transformation has never been reported to occur in children with VLS.

Progression to carcinoma has not been reported in children, although there have been several case reports of vulvar melanoma in association with pediatric VLS [35]. Early onset squamous malignancy has also been reported in adult life when VLS first appeared in childhood [5].

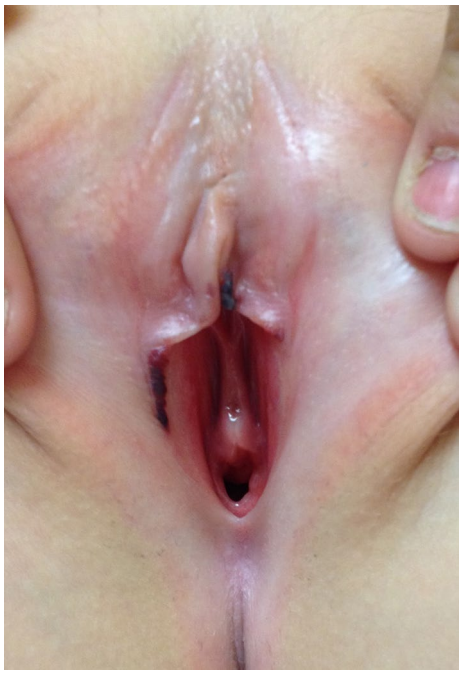

Fig. 6 Lichen sclerosus in a child characterized by pallor, purpura and erosions

3.5 Clinical Presentation in Children

A recent study of 70 children with VLS showed the mean age of development of symptoms was 5.0 years (range 1–12 years) and the mean age at diagnosis was 6.7 years (range 3–14 years) [5]. Another study of 46 children found the mean age of diagnosis to be 7.8 years, with a delay in diagnosis of 1.6 years [36]. Both studies indicate that many children suffer for long periods of time before being diagnosed and treated. They also reported the most common presenting symptoms were itching and soreness; however, other symptoms or noted signs at presentation are purpura, bleeding, dysuria, constipation, genital erosions and extragenital lesions. In one study, less than 10% of the children studied were asymptomatic and were discovered after biopsy for another reason [36]. Although children present with itch and pain, about two thirds also report dysuria and pain with defecation, leading to constipation [37]. These presentations are quite different to adults, who normally present with itch and dyspareunia. It is not uncommon for children with VLS to be referred to urologists and gastroenterologists [37].

If purpura is present, children with VLS have been reported to be referred to child protection units [38]. However, in VLS, purpura may occur without significant trauma, and indeed, when purpura is caused by physical damage in normal vulvar skin, it resolves quickly, unlike the purpura of LS that is persistent (Fig. 6).

The morphology of VLS in children does not differ from adults. Older texts describe a figure of eight appearance encircling the vulva and perianal skin, but any part of the vulva, perineum and perianal skin may be affected individually. Scarring also occurs in children, and in rare circumstances, a child will present with loss of architecture without the typical epithelial changes. Fissuring is common and responsible for pain [36].

3.6 The Course of the Disease in Children

As in adults, if VLS is not treated in a child, progressive loss of the vulvar architecture occurs [36]. The child may not ever develop labia minora, and the clitoris may be buried [25]. The clitoral hood may become non-retractile.

Although squamous malignancy has not been reported in children, a study has shown that although human papillomavirus (HPV) in children with VLS is not found more frequently than in controls, when it is found, oncogenic HPV genotypes are more common than in children without VLS, and this raises questions about long-term cancer risk [39].

Older reports have suggested that LS in children will resolve at or after puberty. However, this is not always the case, and there are now studies that show that whilst there may be improvement, true remission cannot be assumed [6]. One study has shown that at least 75% of girls still have ongoing symptoms and signs [7].

As in adults, the course of the disease can be modified by treatment [37]. A confounding problem in VLS is the adolescent years. During this time, in the authors' experience,

compliance issues often arise linked to embarrassment and refusal to be examined or aided by a parent. Even the most trusting doctor–patient relationship may flounder at this time.

Further, compliance can be a problem in managing children when parents are unwilling or unable to supervise. When treatment is left entirely to small children, it is understandable that it may be sub-optimally applied.

4 Differential Diagnosis

The differential diagnosis in adults includes lichenification, most often associated with dermatitis in atopic individuals, extramammary Paget's disease, genital warts, vitiligo, non-pigmented seborrhoeic keratosis and vulvar intraepithelial neoplasia. Lichen planus can be difficult to differentiate, and the scarring associated with it may simulate end-stage LS. Graft-versus-host disease and mucosal pemphigoid have more in common clinically with lichen planus than VLS, but are also scarring conditions. Additionally, VLS may co-exist with lichen planus, producing a confusing clinical picture [25].

When psoriasis co-exists with VLS, the clinical picture is also confusing as the skin may not appear white, and the clue is the textural change, which may be subtle. Similarly, when it co-exists with vitiligo, textural change and loss of architecture will help to differentiate the two conditions clinically. Vitiligo lacks the epithelial changes seen in LS, presenting with sharply marginated white macules that fluoresce under ultraviolet light. In both cases, if there is doubt, a vulvar biopsy will confirm the diagnosis.

In the peri- and post-menopausal group, atrophic changes often co-exist and add some degree of confusion. There may be reduction in the size of the labia minora and pallor of the vestibule due to estrogen deficiency, which can simulate VLS.

The recently described condition vestibular sclerosus is important to differentiate from VLS. This involves only the vestibule and does not have the histological features of LS. There is still some controversy as to whether this condition is a subset of VLS; however, it is not sensitive to corticosteroid treatment [40].

In children, VLS has a characteristic clinical appearance, and there is little to consider in the differential diagnosis other than lichenification and vitiligo. Although lichenified atopic dermatitis can simulate VLS in adults, it is much less likely to do so in children. Vulvar intraepithelial neoplasia, which may have the appearance of a white plaque, has not been reported in pre-pubertal children. Vitiligo in children is usually not hard to differentiate because of a lack of epidermal changes.

It is common to find areas of hyperpigmentation and benign melanocytic proliferation in LS, and these can sometimes simulate melanoma skin cancer [41]. Where VLS is associated with malignancy, the histology is often hyperplastic. However, differentiated vulvar intraepithelial neoplasia may have a subtle appearance and the surrounding LS may lose its pathognomonic hyaline layer [42].

5 Malignancy After Treatment

Extragenital LS and VLS in adults and children have not been reported to be associated with squamous malignancy. Before it was realized that VLS could be adequately treated, there was a significant association with vulvar malignancy and many studies quoted a figure of about 5% lifetime risk. About 60% of vulvar squamous cell carcinomas had histological evidence of adjacent LS [43]. Although a recent guideline has stated that the risk is small, it is not negligible, and some authors have called for lifelong follow-up in all patients [8, 44].

The appearance of a vulvar squamous cell carcinoma can include nodules, persistent fissures, hyperkeratotic plaques, non-healing ulcers and fungating tumors. Any change in an area of LS that does not promptly resolve with potent TCS treatment must be biopsied.

The association of VLS with genital malignancy has very important implications for management. Patients must be aware of the risk, be educated about what to look for, and be regularly treated and followed up.

Anecdotally, experts have long suspected that adequately treated VLS might have a malignancy rate much lower than 5%. The suggestion has therefore been made that the risk of malignancy is reduced in uncomplicated VLS that had been diagnosed and treated appropriately [45]. A prospective study of VLS in 507 adult women compared patients who adhered to treatment and those who did not. It demonstrated that TCS treatment that kept the skin objectively normal also resulted in minimal scarring and greatly reduced the risk of cancer [9]. Other authors had previously suspected this, but it had not been confirmed [45, 46].

6 Management

VLS in adults is a lifelong disease that is unlikely to remit. Most patients are unable to stop treatment without eventual relapse, although this may take many months. It is important when counseling to emphasize that treatment should be assumed to be for life [46].

In the unusual instances where patients have apparently remitted, they need to be kept under long-term observation

as, in the authors' experience, VLS can re-activate after years of dormancy.

6.1 Severity Grading and Treatment Stratification

Before making a decision about treatment, it is important to decide on the severity of VLS. In general, the severity of a skin condition can be determined by a combination of the inherent observed severity of the disease and its impact on quality of life. This will give a global impression, but in terms of treatment selection in VLS, it is the degree of hyperkeratosis that can be modified by medical treatment [9]. Following response, there is usually return of function and reduction in life impact. Although fusion may partially reverse, scarring is not affected by medical treatment, and surgical management is usually required if there is functional impairment. In the author's experience, not all scarring results in loss of function, particularly if the patient is not sexually active.

As yet there has not been a study that has resulted in a universally accepted severity grade. However, two studies have suggested a grade of hyperkeratosis as a guide to choice of topical therapy [40, 47].

6.2 Topical Therapy

There are two phases of treatment for VLS:

1. Induction of remission, carried out over a period of up to a year.
2. Maintenance treatment, which is lifelong.

It is now accepted that potent TCS is the gold standard for obtaining remission in VLS. The first report of this treatment was published in 1991 (clobetasol propionate 0.05%, a 'super-potent' TCS) and many others followed [32, 47, 48]. Until that report [32], it had been considered unthinkable to apply such strong TCS to genital skin and treatment regimens with weak TCS, testosterone and progesterone were used. As a result, VLS was considered very difficult to treat.

Once it was shown that potent TCS was effective and safe, VLS became one of the easiest vulvar conditions to manage. Many further studies with potent and super-potent TCS have confirmed this as a safe and highly effective treatment in children and adults [31, 44, 49].

VLS is in fact so responsive to TCS that failure to improve should be reason to suspect that the diagnosis is wrong, the patient is not using the treatment or there are other factors confounding symptomatic response, such as malignancy, allergy, superinfection or estrogen deficiency. In rare cases of severe hyperkeratotic disease, however, even potent TCS alone can be inadequate to achieve complete control [50].

Initially, most published data were focused on clobetasol propionate, with more recent studies comparing its efficacy with that of mometasone furoate 0.1% [48]. However, it should not be assumed that VLS can only be treated by these two products, and in almost all cases, other TCS of similar potency will produce good outcomes [8, 51]. The clinician should first decide if the lesions are more or less hyperkeratotic, and match the potency of the topical steroid to the severity of the skin disease [9]. There is no one preparation that is superior to the other; the relative severity and choice of treatment appropriate to it is what is relevant to management [9]. In general terms, medications in ointment bases rather than creams tend to be better tolerated and more effective on the vulva. This has been documented in a recent study [52].

Therefore, in the authors' opinion, the main focus of treatment should not be on the product used, but the end result: attaining and maintaining normal or near to normal skin. There is no single way to do this, and clinicians can make their own judgment relative to the severity of the patient's disease and their preference for daily or intermittent treatment. Many patients relate that daily regimens are easier to recall than intermittent ones. Regular follow-up encourages ongoing compliance.

6.3 Induction of Remission

Regimes to induce remission vary, but the common theme is that a potent or super-potent TCS should be used initially. There is no single way to induce remission, and therapy should be guided by individual response.

A recent study recommended the following [9]:

- Severely hyperkeratotic disease (very thick, white plaque): ultra-potent TCS (clobetasol propionate 0.05% ointment) twice daily until itching has ceased (usually 1–2 weeks) then daily until review at 6 weeks.
- Hyperkeratotic disease (moderately thick white plaque): super-potent TCS (e.g., betamethasone dipropionate 0.05% or mometasone furoate 0.1%) twice daily until itching has ceased then daily until review at 6 weeks.
- Mild disease with only pallor and very little hyperkeratosis: moderate potency TCS (e.g., triamcinolone acetonide 0.02%, methylprednisolone aceponate 0.1%) daily until review at 6 weeks.

When a potent TCS is used on the vulva, it is important to review the patient at around 6 weeks of treatment to assess effect and tolerability. Patients may not have understood how important ongoing treatment is initially, and this visit is an opportunity to emphasize this. Patients are usually feeling much better and many assume they are cured. It is important to emphasize that treatment must now be maintained and

to explain that the reason for this is to prevent cancer and scarring.

The initial potency of TCS is continued until the skin texture and color has returned to normal or as close to normal as possible. There may be residual hyper- or hypopigmentation; however, the texture of the surface of the skin usually improves markedly. Once this has been achieved, patients progress to maintenance therapy. Symptom resolution occurs quickly, but resolution of abnormal signs takes longer. Patients must therefore continue their regular treatment even after symptom resolution.

6.4 Long-Term Management

Although the correct diagnosis and initial management of VLS is of great importance, treatment does not stop there, and indeed it is long-term control that ensures the safety of the patient [9].

Regimens for maintenance treatment are difficult to research because of the challenges of conducting a long-term follow-up study. Typically, reviews and published articles state that the condition does not spontaneously resolve and has to be controlled; however, there is no consensus on what this long-term control involves [53–55]. A recent guideline stated in its introduction that "Treatment remains unsatisfactory particularly in women as disabling scar formation is common despite treatment." The same review stated that treatment aimed chiefly for suppression of symptoms and that proactive management *may* be considered to maintain remission, if needed, in active disease. No specific recommendation was made [56].

A Cochrane review has stated that there is insufficient data to make recommendations on long-term management and called for a study of approximately 2000 women, with half in an untreated control group to determine whether treatment could prevent malignancy, but knowing the possible complications of lack of treatment, this is difficult to condone ethically [49].

The time taken to achieve remission of VLS is variable, but in the authors' experience, it is usually around 3–6 months of continual potent TCS treatment. The weakness of most published studies is that they observe patients for the first 3–6 months only. Long-term observational studies of adequate numbers of treated patients are few. For most publications, the longest period of observation documented is 3 years.

There are three exceptions: a descriptive cohort study from the UK, with a mean length of follow-up of 66 months, a long-term study from France, which was conducted prospectively over 10 years, and a study from Australia conducted prospectively over 8 years [9, 45, 46]. This latter study of 507 women is the best evidence we have to confirm what most experienced practitioners know: that although TCS easily induces remission, it does not cure VLS. Furthermore, the French study reported an 84% recurrence rate if treatment was ceased.

These studies suggest that treatment might change the course of the disease, reducing the risk of cancer and scarring. The Australian observational study provided compelling evidence that this is the case [9]. In this study, patients were reviewed every 3–6 months and the potency of the TCS was slowly titrated down to a moderate to mild potency for maintenance therapy. This was achievable in about 75% of patients. The rest required long-term therapy with more potent TCS.

The maintenance regimen used in the French and UK studies was intermittent clobetasol propionate 1–3 times a week, and this is what most other published papers have stated ever since. However, there is no single way to treat VLS long term, because differing degrees of severity require different regimes. What is important is to achieve an outcome of maintenance of normal skin texture and color.

The main problems that have been postulated with long-term use of TCS on the genital area are TCS-related atrophy, peri-orificial dermatitis and *Candida* superinfection. In practice, only peri-orificial dermatitis is common and is frequently asymptomatic as long as the TCS dose is titrated to severity.

Interestingly, the French and UK studies and another from the UK with a 3-year follow-up period [51] recorded that side effects were rare when treating VLS with TCS. This was confirmed by an Australian study where side effects were minimal and reversible and were confined to skin fragility and erythema [9]. The argument that long-term TCS would produce atrophy is therefore not valid in VLS.

In practice, a treatment review every 6 months will determine the lowest maintenance regimen that will ensure continuing remission. TCS treatment is constantly titrated to degree of hyperkeratosis. If this relapses, the strength of treatment increases. If atrophy or corticosteroid dermatitis occurs, it is reduced. Managing patients with VLS long term with TCS has been shown to be safe, inexpensive and effective [57]. None of the compliant patients in the Australian study developed a cancer and over 95% had no further disease progression or scarring. Over 90% had complete and sustained symptom control, and in those who were sexually active, over 90% no longer experienced dyspareunia. For the majority, good compliance was easily achieved.

In the light of this study, regimens that are used on an "as needed" basis to control symptoms only may need to be re-evaluated [34]. Symptom control in VLS is not difficult to achieve, but objective disease suppression should be the target outcome or the patient is still at risk of complications. It is a common theme amongst patients who have succumbed to cancer or disease progression as a result of poor compliance with treatment that they had remained asymptomatic.

In children, a recent retrospective study of 46 children with VLS, comparing compliant patients with non-compliant ones, showed that when normal skin is attained and maintained, progression of the disease ceased and scarring and atrophy did not occur. Scarring that was present prior to treatment, however, did not reverse [36].

A recommended long-term follow-up regimen from the Australian study is:

- Patients are reviewed every 6 months until they have been in a stable remission for 2 years, then yearly with the proviso that they have an examination by their general practitioner half way through that year and come back earlier if they have any concerns.
- If evidence of relapse occurs on treatment, more potent corticosteroid is used until this settles.
- If there is evidence of corticosteroid excess, less is used. Corticosteroid excess usually evidences itself with vulvar redness and burning or fragility. This reverses quickly once treatment is adjusted.
- Patients should be encouraged not to stop treatment once they are in remission, but to continue with the lowest dose of corticosteroid possible to maintain complete objective normality. The psychological impact of a recurrence on a patient who is finally in remission after years of suffering can be devastating. Furthermore, patients who do not comply with treatment have a 50% risk of scarring and a 5% risk of development of malignancy. Each review is an opportunity to remind your patients of the importance and safety of maintenance treatment.

The main outcome measures of treatment should be:

- Symptom control: no itch or soreness is expected.
- Ability to have intercourse: in post-menopausal women this may also require topical estrogen to reduce vaginal dryness.
- Prevention of scarring, fusion and loss of clitoral substance. (Reduction in labia minora after menopause is common, not problematic, but not always prevented by treatment.)
- Prevention of malignancy.
- Lack of side effects.

6.5 Side Effects of Treatment

- Candidiasis: this is easily controlled with antifungal therapy.
- Erythema: this responds rapidly to a reduction in corticosteroid strength.
- Stinging from topical therapy: this usually settles as fissures and erosions heal. It is virtually always possible to find a well-tolerated TCS.

Some patients may have recalcitrant thickened areas that appear non-responsive even to super-potent corticosteroid. These should always be biopsied to rule out malignancy. Such lesions may respond to intralesional corticosteroid if they are causing distress [58].

The most important principle is to maintain follow-up to maintain treatment and detect complications. It has been argued by some authors that this approach is unnecessary in uncomplicated disease [44, 59]. A study from the UK has shown that once a patient leaves the specialist, VLS is not well followed up in general practice [60]. VLS is not common, and the cost of even one patient with a vulvar cancer or the need for surgery for scarring might be compared to the cost of follow-up of many to ensure that cancer does not occur and scarring does not progress.

6.6 Other Topical Therapies

Topical immunosuppressive agents, such as tacrolimus and pimecrolimus have been described as potentially playing a role in the treatment of VLS in children and adults [61].

There has been one phase II trial to assess the safety and efficacy of tacrolimus ointment 0.1% for the treatment of VLS, and the results were released in 2006. Clearance of active LS was reached by 43% of patients at 24 weeks of treatment and partial resolution was reached in a further 34% of patients. Maximal effects of therapy occurred between weeks 10 and 24 of treatment [62]. The authors who recommend topical immunosuppressives state that these agents are less likely to cause atrophy. However, atrophy is in fact rare from TCS, and when it occurs, it invariably improves with a lower dose.

While there were no adverse events during the 18 months of follow-up, the theoretical disadvantage of topical immunosuppressive agents is an increased risk of malignant transformation due to local immunosuppression. This is arguably an important consideration given the well-described association of VLS and malignancy. Squamous cell carcinoma has been reported in adults with VLS in association with pimecrolimus treatment [63].

At the time of writing, there is insufficient data to recommend topical immunosuppressive agents to treat LS and no justification when TCS is effective and safe. Topical immunosuppressive agents have no advantage over TCSs. They are more expensive, very likely to sting and burn, and their long-term safety is not established.

Topical tretinoin has been used in VLS as monotherapy, but evidence is lacking and treatment is possibly limited by irritancy [64].

Historically, topical testosterone has been used to treat VLS, but currently, there is no longer any role for it, with more effective treatments available and as it may produce androgenization in girls [65].

Similarly, topical estrogen is of no value, other than to reduce hypo-estrogenic atrophy in post-menopausal women. This in fact is an important aspect of managing post-menopausal women with VLS, but in itself is not a specific treatment. However, ongoing pain from vaginal dryness and fragility which are part of the genitourinary syndrome of menopause may make it hard to assess outcomes of treatment for concurrent VLS and should therefore be addressed concurrently.

6.7 Physical Therapy: Surgery, Laser, Phototherapy, Photodynamic Therapy, Intralesional Corticosteroid and Lipo-Injection

Historically, vulvectomy has been performed in adults for VLS, but the disease recurs despite this. This is no longer considered an acceptable method of treatment and is completely contraindicated.

Various surgical procedures have been used to treat labial and periclitoral adhesions. Simple division of adhesions gives a very satisfactory result, provided that potent TCS are used daily post-operatively until healing is complete. Unless this is done, re-fusion is likely [66]. It is sometimes necessary to apply the post-operative steroid on a dilator. Surgery is rarely appropriate therapy in the pediatric population unless significant fusion of the labia has occurred.

Newer treatments for very recalcitrant hyperkeratotic VLS include intralesional platelet-rich plasma [67]. There have been no published trials. Similarly lipo-injection has received some attention, but convincing clinical trials are lacking [68].

In some patients with hyperkeratotic disease, ablative laser treatment can be a useful adjunct to treatment, but is not a substitute for topical therapy, which must be continued subsequently to maintain clinical response [50].

Phototherapy including photodynamic therapy has been reported to be effective [69, 70], and the authors have found narrow-band UVB to be effective as an adjunct in recalcitrant cases. However, phototherapy to the genital area is difficult and not always practical. There are no clinical trials to support it. There has, however, been a report of successful treatment of extragenital LS with narrow-band UVB [71]. A concern with treating a condition with a malignancy risk with phototherapy is that this may be potentiated.

6.8 Systemic Therapy

It is rare for VLS to be so refractory to treatment that systemic therapy would be required. There is some evidence that methotrexate combined with pulsed corticosteroid can be effective in severe generalized LS; however, this has never been extended to use in VLS [72].

There is no evidence that hydroxychloroquine or systemic retinoids are useful.

7 The Effect of Lichen Sclerosus on Quality of Life and Sexual Activity

VLS has a major impact on quality of life [73]. This is not always improved simply by treating the skin disease. Returning the skin to normal in VLS does not always ensure that the impact on the patient has been reduced. Although pain and itch may have resolved, patients often have ongoing issues: the need for maintenance treatment and regular examinations can in itself be a burden, particularly for children and their families. Concerns about the future, particularly relationships, pregnancy and cancer can affect them greatly emotionally.

In the authors' experience, patients with VLS can usually resume sexual activity with treatment. In postmenopausal women, this is complicated by changes related to genitourinary syndrome of menopause, and in those with significant scarring, normal sexual activity may not be possible until this has been corrected surgically.

In women who have had a long history of painful sex, there may be significant pelvic floor spasm, and physiotherapy to overcome this may be needed. Some develop an aversion to sexual intercourse and need psychological help. There are those who decline any help, because their lack of interest in sex has been legitimized by their disease [74].

In general, it should be possible to return almost all motivated patients to a normal life as long as a regime can be found that they find acceptable and easy to comply with.

8 Conclusion

Although the etiology of VLS remains unknown, knowledge of how to manage it has progressed in the last 5 years. Once thought a difficult to manage condition with a poor prognosis, it has emerged that with regular TCS treatment patients can remain well, returning to a state of normal wellbeing for long periods of time and that the course of the disease can indeed be modified by treatment, which is safe and effective in the long term.

Compliance with Ethical Standards

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References

1. Fischer GO. The commonest causes of symptomatic vulvar disease: a dermatologist's perspective. Australas J Dermatol. 1996;37:12–8.
2. Goldstein AT, Marinoff SC, Christopher K, Srodon M. Prevalence of vulvar lichen sclerosus in a general gynecology practice. J Reprod Med. 2005;50:477–80.
3. Bleeker MC, Visser PJ, Overbeek LI, van Beurden M, Berkhof J. Lichen sclerosus: incidence and risk of vulvar squamous cell carcinoma. Cancer Epidemiol Biomarkers Prev. 2016;25:1224–30.
4. Tong LX, Sun GS, Teng JM. Pediatric lichen sclerosus: a review of the epidemiology and treatment options. Pediatr Dermatol. 2015;32:593–9.
5. Powell J, Wojnarowska F. Childhood vulvar lichen sclerosus: an increasingly common problem. J Am Acad Dermatol. 2001;44:803–6.
6. Smith SD, Fischer G. Childhood onset vulvar lichen sclerosus does not resolve at puberty: a prospective case series. Pediatr Dermatol. 2009;26:725–9.
7. Powell J, Wojnarowska F. Childhood vulvar lichen sclerosus. The course after puberty. J Reprod Med. 2002;47:706–9.
8. Micheletti L, Preti M, Radici G, et al. Vulvar lichen sclerosus and neoplastic transformation: a retrospective study of 976 cases. J Low Genit Tract Dis. 2016;20:180–3.
9. Lee A, Bradford J, Fischer G. Long-term management of adult vulvar lichen sclerosus: a prospective cohort study of 507 women. JAMA Dermatol. 2015;151:1061–7.
10. 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. Arch Dermatol. 2008;144:1432–5.
11. Harrington CI, Dunsmore IR. An investigation into the incidence of auto-immune disorders in patients with lichen sclerosus and atrophicus. Br J Dermatol. 1981;104:563–6.
12. Kyriakis KP, Emmanuelides S, Terzoudi S, et al. Gender and age prevalence distributions of morphea en plaque and anogenital lichen sclerosus. J Eur Acad Dermatol Venereol. 2007;21:825–6.
13. Hofer MD, Meeks JJ, Mehdiratta N, et al. Lichen sclerosus in men is associated with elevated body mass index, diabetes mellitus, coronary artery disease and smoking. World J Urol. 2014;32:105–8.
14. Simpkin S, Oakley A. Clinical review of 202 patients with vulval lichen sclerosus: a possible association with psoriasis. Australas J Dermatol. 2007;48:28–31.
15. Jacobs L, Gilliam A, Khavari N, Bass D. Association between lichen sclerosus and celiac disease: a report of three pediatric cases. Pediatr Dermatol. 2014;31:e128–31.
16. Chakhtoura Z, Vigoureux S, Courtillot C, et al. Vulvar lichen sclerosus is very frequent in women with Turner syndrome. J Clin Endocrinol Metab. 2014;99:1103–4.
17. Oyama N, Chan I, Neill SM, et al. Autoantibodies to extracellular matrix protein 1 in lichen sclerosus. Lancet. 2003;362:118–23.
18. Birenbaum DL, Young RC. High prevalence of thyroid disease in patients with lichen sclerosus. J Reprod Med. 2007;52:28–30.
19. Sherman V, McPherson T, Baldo M, et al. The high rate of familial lichen sclerosus suggests a genetic contribution: an observational cohort study. J Eur Acad Dermatol Venereol. 2010;24:1031–4.
20. Gao XH, Barnardo MC, Winsey S, et al. The association between HLA DR, DQ antigens, and vulval lichen sclerosus in the UK: HLA DRB112 and its associated DRB112/DQB10301/04/09/010 haplotype confers susceptibility to vulval lichen sclerosus, and HLA DRB10301/04 and its associated DRB10301/04/DQB10201/02/03 haplotype protects from vulval lichen sclerosus. J Invest Dermatol. 2005;125:895–9.
21. Gambichler T, Terras S, Kreuter A, Skrygan M. Altered global methylation and hydroxymethylation status in vulvar lichen sclerosus: further support for epigenetic mechanisms. Br J Dermatol. 2014;170:687–93.
22. Van de Nieuwenhof HP, Meeuwis KA, Nieboer TE, et al. The effect of vulvar lichen sclerosus on quality of life and sexual functioning. J Psychosom Obstet Gynaecol. 2010;31:279–84.
23. Byren I, Venning V, Edwards A. Carcinoma of the vulva and asymptomatic lichen sclerosus. Genitourin Med. 1993;69:323–4.
24. Zendell K, Edwards L. Lichen sclerosus with vaginal involvement: report of 2 cases and review of the literature. JAMA Dermatol. 2013;149:1199–202.
25. Yahiro C, Oka M, Fukunaga A, et al. Mucosal lichen sclerosus/lichen planus overlap syndrome with cutaneous lesions of lichen sclerosus. Eur J Dermatol. 2016;26:204–5.
26. Owen CM, Yell JA. Genital lichen sclerosus associated with incontinence. J Obstet Gynaecol. 2002;22:209–10.
27. Borghi A, Corazza M, Minghetti S, et al. Dermoscopic features of vulvar lichen sclerosus in the setting of a prospective cohort of patients: new observations. Dermatology. 2016;232:71–7.
28. Dell EA, Miest RYN, Lohse CM, Torgerson RR. Vulvar neoplasms in 275 women with genital lichen sclerosus and impact of treatment: a retrospective chart review. J Eur Acad Dermatol Venereol. 2018. https://doi.org/10.1111/jdv.14938 **(Epub ahead of print)**.
29. Te Grootenhuis NC, Pouwer AW, de Bock GH, et al. Prognostic factors for local recurrence of squamous cell carcinoma of the vulva: a systematic review. Gynecol Oncol. 2018;148:622–31.
30. Jones RW, Sadler L, Grant S, et al. Clinically identifying women with vulvar lichen sclerosus at increased risk of squamous cell carcinoma: a case-control study. J Reprod Med. 2004;49:808–11.
31. van der Meijden WI, Boffa MJ, Ter Harmsel WA, et al. 2016 European guideline for the management of vulval conditions. J Eur Acad Dermatol Venereol. 2017;31:925–41.
32. Nguyen Y, Bradford J, Fischer G. Lichen sclerosus in pregnancy: a review of 33 cases. J Invest Dermatol. 2017;137:S197.
33. Dalziel KL, Millard PR, Wojnarowska F. The treatment of vulval lichen sclerosus with a very potent topical steroid (clobetasol propionate 0.05%) cream. Br J Dermatol. 1991;124:461–4.
34. Lee A, Bradford J, Fischer G. Evidence-based (S3) guideline on (anogenital) lichen sclerosus. JEADV. 2015;29(10):e1–43 **(J Eur Acad Dermatol Venereol. 2017;31:e57–e58)**.
35. La Spina M, Meli MC, De Pasquale R, et al. Vulvar melanoma associated with lichen sclerosus in a child: case report and literature review. Pediatr Dermatol. 2016;33:e190–4.
36. Ellis E, Fischer G. Prepubertal-onset vulvar lichen sclerosus: the importance of maintenance therapy in long-term outcomes. Pediatr Dermatol. 2015;32:461–7.
37. Smith SD, Fischer G. Paediatric vulval lichen sclerosus. Australas J Dermatol. 2009;50:243–8.
38. Wood PL, Bevan T. Lesson of the week child sexual abuse enquiries and unrecognised vulval lichen sclerosus et atrophicus. BMJ. 1999;319:899–900.
39. Powell J, Strauss S, Gray J, Wojnarowska F. Genital carriage of human papilloma virus (HPV) DNA in prepubertal girls with and without vulval disease. Pediatr Dermatol. 2003;20:191–4.
40. Day T, Burston K, Dennerstein G, et al. Vestibulovaginal sclerosis versus lichen sclerosus. Int J Gynecol Pathol. 2017. https://doi.org/10.1097/pgp.0000000000000441 **(Epub ahead of print)**.
41. Carlson JA, Mu XC, Slominski A, et al. Melanocytic proliferations associated with lichen sclerosus. Arch Dermatol. 2002;138:77–87.
42. Sideri M, Jones RW, Wilkinson EJ, et al. Squamous vulvar intraepithelial neoplasia: 2004 modified terminology, ISSVD vulvar oncology subcommittee. J Reprod Med. 2005;50:807–10.
43. Powell JJ, Wojnarowska F. Lichen sclerosus. Lancet. 1999;353:1777–83.

44. Lewis FM, Tatnall FM, Velangi SS, et al. British Association of Dermatologists guidelines for the management of lichen sclerosus, 2018. Br J Dermatol. 2018;178:839–53.
45. Cooper SM, Gao XH, Powell JJ, Wojnarowska F. Does treatment of vulvar lichen sclerosus influence its prognosis? Arch Dermatol. 2004;140:702–6.
46. Renaud-Vilmer C, Cavelier-Balloy B, Porcher R, Dubertret L. Vulvar lichen sclerosus: effect of long-term topical application of a potent steroid on the course of the disease. Arch Dermatol. 2004;140:709–12.
47. Bradford J, Fischer G. Long-term management of vulval lichen sclerosus in adult women. Aust N Z J Obstet Gynaecol. 2010;50:148–52.
48. Corazza M, Borghi A, Minghetti S, et al. Clobetasol propionate vs. mometasone furoate in 1-year proactive maintenance therapy of vulvar lichen sclerosus: results from a comparative trial. J Eur Acad Dermatol Venereol. 2016;30:956–61.
49. Chi CC, Kirtschig G, Baldo M, et al. Topical interventions for genital lichen sclerosus. Cochrane Database Syst Rev. 2011. https://doi.org/10.1002/14651858.CD008240.pub2.
50. Lee A, Lim A, Fischer G. Fractional carbon dioxide laser in recalcitrant vulval lichen sclerosus. Australas J Dermatol. 2016;57:39–43.
51. Sinha P, Sorinola O, Luesley DM. Lichen sclerosus of the vulva. Long-term steroid maintenance therapy. J Reprod Med. 1999;44:621–4.
52. Corazza M, Virgili A, Toni G, Borghi A. Mometasone furoate in the treatment of vulvar lichen sclerosus: could its formulation influence efficacy, tolerability and adherence to treatment? J Dermatolog Treat. 2018;29(3):305–9.
53. Funaro D. Lichen sclerosus: a review and practical approach. Dermatol Ther. 2004;17:28–37.
54. Tasker GL, Wojnarowska F. Lichen sclerosus. Clin Exp Dermatol. 2003;28:128–33.
55. Val I, Almeida G. An overview of lichen sclerosus. Clin Obstet Gynecol. 2005;48:808–17.
56. Kirtschig G, Cooper S, Aberer W, et al. Evidence-based (S3) guideline on (anogenital) lichen sclerosus. J Eur Acad Dermatol Venereol. 2017;31(2):e81–3.
57. Kai A, Lewis F. Long-term use of an ultrapotent topical steroid for the treatment of vulval lichen sclerosus is safe. J Obstet Gynaecol. 2016;36:276–7.
58. Mazdisnian F, Degregorio F, Mazdisnian F, Palmieri A. Intralesional injection of triamcinolone in the treatment of lichen sclerosus. J Reprod Med. 1999;44:332–4.
59. Jones RW, Scurry J, Neill S, MacLean AB. Guidelines for the follow-up of women with vulvar lichen sclerosus in specialist clinics. Am J Obstet Gynecol. 2008;198:496.e1–3.
60. Balasubramaniam P, Lewis FM. Long-term follow-up of patients with lichen sclerosus: does it really happen? J Obstet Gynaecol. 2007;27:282.
61. Funaro D, Lovett A, Leroux N, Powell J. A double-blind, randomized prospective study evaluating topical clobetasol propionate 0.05% versus topical tacrolimus 0.1% in patients with vulvar lichen sclerosus. J Am Acad Dermatol. 2014;71:84–91.
62. 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. Br J Dermatol. 2006;155:1021–8.
63. Fischer G, Bradford J. Topical immunosuppressants, genital lichen sclerosus and the risk of squamous cell carcinoma: a case report. J Reprod Med. 2007;52:329–31.
64. Borghi A, Corazza M, Minghetti S, Virgili A. Topical tretinoin in the treatment of vulvar lichen sclerosus: an advisable option? Eur J Dermatol. 2015;25:404–9.
65. Sideri M, Origoni M, Spinaci L, Ferrari A. Topical testosterone in the treatment of vulvar lichen sclerosus. Int J Gynaecol Obstet. 1994;46:53–6.
66. Bradford J, Fischer G. Surgical division of labial adhesions in vulvar lichen sclerosus and lichen planus. J Low Genit Tract Dis. 2013;17:48–50.
67. Goldstein AT, King M, Runels C, et al. Intradermal injection of autologous platelet-rich plasma for the treatment of vulvar lichen sclerosus. J Am Acad Dermatol. 2017;76:158–60.
68. Boero V, Brambilla M, Sipio E, et al. Vulvar lichen sclerosus: a new regenerative approach through fat grafting. Gynecol Oncol. 2015;139:471–5.
69. Criscuolo AA, Schipani C, Cannizzaro MV, et al. New therapeutic approaches in the treatment of anogenital lichen sclerosus: does photodynamic therapy represent a novel option? G Ital Dermatol Venereol. 2017;152:117–21.
70. Shi L, Miao F, Zhang LL, et al. Comparison of 5-aminolevulinic acid photodynamic therapy and clobetasol propionate in treatment of vulvar lichen sclerosus. Acta Derm Venereol. 2016;96:684–8.
71. Colbert RL, Chiang MP, Carlin CS, Fleming M. Progressive extragenital lichen sclerosus successfully treated with narrowband UV-B phototherapy. Arch Dermatol. 2007;143:19–20.
72. Kreuter A, Tigges C, Gaifullina R, et al. Pulsed high-dose corticosteroids combined with low-dose methotrexate treatment in patients with refractory generalized extragenital lichen sclerosus. Arch Dermatol. 2009;145:1303–8.
73. Haefner HK, Aldrich NZ, Dalton VK, et al. The impact of vulvar lichen sclerosus on sexual dysfunction. J Womens Health (Larchmt). 2014;23:765–70.
74. Harris V, Fischer G, Bradford JA. The aetiology of chronic vulval pain and entry dyspareunia: a retrospective review of 525 cases. Aust N Z J Obstet Gynaecol. 2017;57:446–51.