




GUIDELINE

2021 European guideline for the management of vulval conditions

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Conflicts of interest

Dr Boffa is President, Maltese Association of Dermatology & Venereology and Elected member of Malta Medical Council. Dr Lewis has received royalties for contribution to textbooks A Practical Guide to Vulval Disease. Ridley's 'The Vulva' 3rd edition and honoraria for teaching on dermatology. She is a Council member of the European College for the Study of Vulval Disease. Professor Tiplica has received lecture honoraria from Antibiotice SA and Novartis Pharma. He is chair of IUSTI Europe and president of the Romanian Association of Dermato-Venereologists. Dr Sherrard is a Member of the European Sexually Transmitted Infections Guidelines Editorial Board; and she is an officer of the International Union against Sexually Transmitted Infections (membership secretary). She is UK representative to the EBDV at UEMS. The other authors declare no conflict of interest.

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Changes to this guideline since the 2015 version:

- Evaluation scale for genital psoriasis lesions
- Use of ixekizumab, secukinumab and ustekinumab in treating genital psoriasis
- Diagnostic criteria for vulval lichen planus
- Changed first line management recommendations for vulvodynia

Search strategy

- Guidelines produced by the British Association for Sexual Health and HIV (www.bashh.org) were reviewed.
- Searched libraries: MEDLINE, MEDLINE process, Embase, Cochrane library.
- Search up to June 2021 with no date limitation. The search strategy comprised the following terms in the title or abstract: Vulval lichen sclerosus, Vulval lichen planus, Vulval eczema, Vulval lichen simplex, Vulval psoriasis, Vulval intraepithelial neoplasia, High-grade SIL of the vulva, vulval HSIL, Vulval pain syndromes/vulvodynia.

Scope

This guideline covers the more common conditions affecting the vulva:

- 1 Vulval dermatitis (eczema)
- 2 Psoriasis
- 3 Lichen simplex chronicus
- 4 Lichen sclerosus
- 5 Lichen planus
- 6 Vulvodynia
- 7 Vulval intraepithelial neoplasia (VIN)

General advice for delivery of vulval care

Vulval conditions may present to a variety of clinicians including dermatologists, genitourinary medicine physicians, gynaecologists and primary care physicians or general practitioners (GP). Investigations and management span across this spectrum, so women with vulval conditions are best managed by a multidisciplinary approach, which includes clear referral pathways between disciplines or access to a specialist multidisciplinary

vulval service. There should also be access to clinico- pathological services to allow discussion and review of histology results.

Physical examination of the patient

Informed consent is a pre-requisite for all examinations, investigations and treatments. Consent is particularly important for intimate examinations of the anogenital area. A chaperone should be offered in all cases and this should be documented clearly in the patient records. The proposed examination should be adequately explained to patients before they undress. All attempts should be made to maintain patients' dignity, providing privacy to dress and undress, and keeping them covered as much as possible. Appropriate facilities and equipment for investigations should be available prior to commencing the examination. The room should be well lit, private and sound-proofed, with a suitable examination couch of adjustable height.¹

Dermatoses and STIs may co-exist or a woman with a pre-existing dermatosis may contract an STI. Screening for sexually transmitted infections (STI) should be considered in all patients, depending on symptoms and risk factors. If the patient presents with vulval itch, particularly with increased discharge, vulvovaginal candidiasis should be excluded. If the symptoms are not relieved by anti-candidal treatment, especially if cultures are negative for candida, then a full genital examination including a speculum examination² should be undertaken unless done recently, and other causes considered. Possible alternate diagnoses include lichen sclerosus, lichen planus, lichen simplex chronicus, psoriasis or a neoplastic condition (particularly HPV-related vulval intra-epithelial neoplasia in young women). Sexual dysfunction should be considered and assessed if appropriate in all patients, either as the cause of the symptoms or developed secondary to the symptoms.

Conditions where STI testing should be specifically considered, is when genital ulcers are present, even in the presence of a dermatosis that causes ulceration. In these cases, testing for herpes simplex and syphilis is recommended. Additionally, where lesions fail to heal with standard treatment, investigations to exclude concurrent STIs should be undertaken.

Cutaneous disorders may be the initial signs of HIV-related immunosuppression and many associated skin diseases are more severe in this group. With the onset of immunosuppression, nonspecific skin changes occur, such as common disorders with atypical clinical features, including numerous hyperkeratotic warts, treatment-resistant seborrheic dermatitis and new or severe psoriasis. HIV testing should be considered in all patients but especially in these presentations.

General advice for all vulval conditions

- Avoid contact with soap, shampoo and bubble bath. Simple emollients can be used as a soap substitute and general moisturizer

- Avoid tight fitting garments which may irritate the area
- Avoid use of spermicidally lubricated condoms and those containing local anaesthetics
- Patients should be given a detailed explanation of their condition, with particular emphasis on any long-term health implications, which should be reinforced by giving them clear and accurate written information about the condition
- Consent should be sought for the patient's GP to be informed about the diagnosis and management.

Topical treatments

- Ointment bases are preferably used on the anogenital skin, because of the reduced need for preservatives in an ointment base, and hence less risk of a secondary contact allergy. Furthermore, cream bases may sting as they contain more water. Regular application of a barrier emollient to the affected areas may protect against local irritants for example urine and menstrual blood.

Sexual partners

- Partner tracing is not required unless screening detects a sexually transmitted infection.

Vulval dermatitis (Eczema)

Dermatitis (also named 'eczema') is an inflammatory reaction characterized histologically by spongiosis, variable acanthosis and a superficial dermal lymphohistiocytic inflammatory infiltrate. The main symptom is itch. Exogenous and endogenous factors can be involved in aetiology.

There is a danger in labelling any erythematous pruritic condition as dermatitis or eczema. Therefore, it is best practice to use the specific diagnosis instead of using these terms, namely atopic dermatitis or irritant/allergic contact dermatitis.³

Aetiology

Atopic dermatitis – there is increasing evidence that this is due to a defect in the barrier function of the skin.⁴ In many atopic individuals, the genital area is spared, but vulval lichen simplex chronicus may be a manifestation of atopic dermatitis, either as isolated vulval disease or in association with disease at other sites.⁵

Irritant contact dermatitis – the commonest type of eczema to affect the vulva. The vulval epithelium is less efficient as a barrier than skin elsewhere⁶ and is in contact with moisture, such as sweat and urine, and prone to friction. Cleansers, fragrances, lubricants and many other topical preparations can exacerbate the symptoms. Irritant dermatitis is a particular problem in those with urinary incontinence.

Allergic contact dermatitis – a type IV delayed hypersensitivity reaction, where the individual has developed an allergy to a

product applied topically. These are commonly fragrances, antibiotics, local anaesthetics and components of some topical treatments.

Seborrhoeic dermatitis – an inflammatory, desquamative dermatosis affecting the scalp, face and more rarely, the trunk. Seborrhoeic dermatitis and psoriasis may be associated and have similar histology. Yeast organisms on the skin may have a role in the development of seborrhoeic dermatitis in predisposed individuals.⁷ This form of dermatitis may have features that are similar to psoriasis but the erythema is much less well-defined.

Symptoms

- Pruritus
- Soreness
- Pain

Signs

- Erythema – this is frequently symmetrical, affecting the labia majora and minora, and extending to the perianal skin and gluteal cleft. In allergic contact dermatitis, this may extend to the thighs.
- Excoriation
- Erosions – if acute
- Serous discharge with oozing and crusting, especially if secondary infection is present
- Keratin debris may build up in the inter-labial sulci
- Lichenification – if chronic

Complications

- Secondary infection
- Development of lichen simplex chronicus

Diagnosis

The diagnosis is usually clinical, based on the clinical history and physical signs. It is helpful to check the rest of the skin for other features of atopic or seborrhoeic dermatitis. The main differential diagnoses are:

- Psoriasis: there are usually well-defined plaques and fissuring is a common feature, which is not seen as frequently in dermatitis. Full skin examination, including the scalp and nails, can give helpful diagnostic clues.
- Candidiasis: this can give a symmetrical, ill-defined erythema, sometimes in the absence of vaginal symptoms. A vulval swab will help to assess this diagnosis.
- Tinea cruris: although rare in women, this should be suspected if there is well-defined, annular or circinate erythema with a papular or pustular edge with peripheral scaling.
- Streptococcus A infection: as a primary or secondary event (superinfection of a pre-existing dermatosis); this can present with symmetrical erythema.

Investigation

A biopsy is rarely necessary but one should be performed if there are atypical features or failure to respond to treatment (**GRADE 1,D**).

Patch testing is useful if an allergic contact dermatitis is suspected, but is not necessary for all types of dermatitis. Patch testing should be performed in a clinic competent in this investigation and interpretation of the results (**GRADE 1,B**). In addition to the standard baseline series of allergens, any patient with a suspected vulval allergic contact dermatitis should be tested to medicaments, preservatives and any specific products applied by the patient to the vulva, at the appropriate dilutions.^{8,9} The relevance of the results must be assessed carefully, as a positive test does not necessarily mean that the tested product is responsible for the vulval rash. Conversely, a negative test cannot completely prove the innocence of a topically applied product.

Appropriate swabs will exclude candidiasis and bacterial infection. Skin scrapings will help to rule out tinea cruris.

Management

- 1 Avoidance of irritants and possible allergens that may be precipitating factors for example cleansers, fragrances and wet wipes. If urinary incontinence is present, then this should be addressed and referral to uro-gynaecology is helpful.
- 2 Use of a bland emollient as a soap substitute for example emulsifying ointment. Barrier preparations are very helpful in those with significant urinary incontinence.
- 3 A topical steroid such as 1% hydrocortisone ointment can be used for mild cases and mometasone furoate or betamethasone valerate 0.025% for more severe disease. This can be applied once daily for 7–10 days until the symptoms and signs settle and can then be used as needed for any recurrent symptoms.
- 4 Treat any co-existing infection with a combination steroid/antifungal or steroid/antibacterial.

Antihistamines may help with sleep disturbance.

Unlicensed treatments Calcineurin inhibitors (topical tacrolimus and pimecrolimus) can be tried for resistant cases, but their use is limited by stinging on application.¹⁰ This stinging may subside with continued use.

Follow-up

Follow-up is not required routinely, but patients who need to use a more potent topical steroid or who have problems in controlling their symptoms should be reviewed.

Patient information

Patients should be given an explanation of their condition and the potential for a recurrence of symptoms. Advice about

hygiene practices that can exacerbate the problem can be linked with useful patient information websites.

Vulval psoriasis

Aetiology

Psoriasis is an immune-mediated disease with genetic predisposition, which involves genital lesions in up to 63% of patients during their lifetime.¹¹ The prevalence of psoriasis in adults ranges from 0.5 to 11.4%.¹² Isolated genital lesions are found in 2–5% of patients.¹³ Several trigger factors are described (some of them present in populations at risk for STI)¹⁴: infections (e.g. streptococcal, HIV), smoking, alcohol excess, physical factors (e.g. tattoos, piercing, trauma) and medication (e.g. systemic steroids, beta-blockers, lithium, non-steroidal anti-inflammatory drugs, antimalarials drugs). Stress is often cited as a triggering factor in medical literature; however, recent studies have found the evidence inconclusive.¹⁵ Main risk factors for developing vulval lesions include disease onset after 20 years of age, scalp and nail lesions, inverse psoriasis, and a higher Psoriasis Activity Score Index (PASI).¹⁶

Vulval psoriasis can be present in patients with psoriasis vulgaris as localized disease or in a disseminated form (also affecting the extensor regions or the gluteal cleft). Vulval involvement can occur in patients with inverse psoriasis (rare cases with involvement of the flexural folds and genitalia). Generalized pustular psoriasis (a rare form of exudative psoriasis) can start spreading from the genital area. Impetigo herpeticiformis is a rare dermatosis of pregnancy with similar pustular lesions that develop from the intertriginous areas (including vulva). Typical onset is during the last trimester of pregnancy with rapid resolution in the postpartum period. Clinically and histologically, it is consistent with pustular psoriasis. Erythrodermic psoriasis is an uncommon form of psoriasis that can cover more than 90% of body surface and be present in the vulval region.

Clinical features

Symptoms

- Vulval pruritus (most frequently reported).¹⁷
- Pain or burning sensation.
- Dyspareunia.¹⁶

Signs

- Monomorphic, symmetrical eruption of erythematous plaques on the vulva. The lesions are well defined, with round margins. Fine silvery scales can be present but are less common at the genitals than at other locations. Lesions on the outer labia majora may be associated with thicker scales compared to the inner sides and labia minora.¹⁸ Psoriatic

plaques can extend to adjacent regions (inguinal, perineal, pubic). Sometimes painful fissures can be present.¹⁹

- In rare cases of generalized pustular psoriasis, pustular lesions may initially occur on erythematous macules that spread from the vulva and other flexural folds to the rest of the body.

Evaluation

Symptoms of genital psoriasis may be evaluated through the Genital Psoriasis Symptoms Scale (GPSS) which includes the patient's assessment of pruritus, pain, discomfort, stinging, burning, redness, scaling and cracking on a 11-point scale.²⁰

Clinical signs may be evaluated through the Static Physicians' Global Assessment of Genitalia (sPGA-G) on a 6-point scale, which includes the assessment of erythema, induration and scales.¹¹

Associated disorders

Psoriatic arthritis²¹ occurs in 15–30% of patients with psoriasis vulgaris or exudative psoriasis. The severity of articular involvement does not correlate with the presence of genital psoriatic lesions.¹⁶ Cardiovascular disease, hypertension, malignancy, diabetes, metabolic syndrome, inflammatory bowel disease or autoimmune diseases can also be associated with psoriasis. In case of HIV patients, psoriasis may be associated with a higher incidence, atypical variants and resistance to treatment.²²

Diagnosis

The diagnosis can usually be made from the clinical history combined with the physical examination, which should include extra-genital sites where psoriasis is common such as the scalp, nails, natal cleft and umbilicus.

Investigation

Dermoscopy may be useful in the evaluation of psoriatic lesions and may reveal the presence of dotted vessels or tortuous capillaries.²³

The histopathological examination is characteristic: parakeratosis, Munro micro-abscesses (neutrophils in the stratum corneum), absent granular cell layer, epidermal hyperplasia, frequent mitoses in the basal cell layer and dilated tortuous capillaries in the dermal papillae.²⁴ Consider investigations for possible associated inflammatory diseases.

Management

General advice The patient should avoid all known trigger factors including scented detergents, synthetic underwear and tight pants.¹⁹

Topical treatment is indicated for localized vulval psoriasis. In patients with disseminated or generalized lesions of psoriasis,

the systemic therapy given is also effective for the genital lesions.²⁵

Due to possible local adverse reactions (mainly irritant), avoid the use of anthralin, tazarotene and ultraviolet therapy when treating vulval psoriasis.¹⁹

Recommended regimens Topical treatment. Treatment will reduce the thickness of the lesions, the degree of erythema and remove scales. All therapeutic possibilities should be presented to obtain a tailored therapy that is acceptable to the patient. If pubic hair is present, the vulval lesions will be better treated with solutions, foams or gels.²⁶ To cover the whole genital area, 0.5 fingertip unit should be sufficient.²⁷

- Topical corticosteroids are recommended in sequential or rotational therapeutic regimens^{28–30}: mid potency topical steroids followed by low potency topical steroids. (**GRADE 1, B**): the duration and frequency will depend on the steroids chosen and the clinical response
- Topical vitamin D analogues are recommended in monotherapy or in combination with topical corticosteroids (**GRADE 1, B**).^{31,32}
- Coal tar preparations (e.g. 1–5% liquor carbonis detergens in aqueous cream) are suggested to be used in mono-therapy or in combination with topical corticosteroids (**GRADE 2, C**).^{31, 33}

Emollients are recommended to reduce local irritation induced by other topical treatment and to maintain the therapeutic results (**GRADE 1, B**).^{31,34}

Systemic treatment. In case of disseminated or generalized psoriasis with genital involvement or in cases of genital psoriasis refractory to topical regimens, systemic therapies may be used, including methotrexate, retinoids, cyclosporine and biological agents. (**GRADE 1, A**).

Depending on each country, National Prescription Protocols for biological agents may approve the initiation of these regimens in patients with isolated genital involvement and a significant functional and quality of life impairment. Ixekizumab (an anti-IL 17A monoclonal antibody) showed improvement of genital erosions, ulcers, fissures, pruritus and sexual life in a randomized, double-blinded placebo-controlled phase 3 trial in 2018.³⁵ Secukinumab (anti-IL 17A monoclonal antibody) showed similar efficacy and safety as ixekizumab in treating genital psoriatic lesions in an open label randomized controlled study in 2021.³⁶ Ustekinumab (an anti-IL 12/23 monoclonal antibody) has proved to be efficient in treating genital psoriasis.³⁷ Guselkumab was used with good results in an observational study conducted to assess its effectiveness and impact on quality of life of patients with genital and facial psoriasis.³⁸

Unlicensed treatments Topical calcineurin inhibitors (tacrolimus, pimecrolimus) are reported to be effective in vulval

psoriasis (**GRADE 2, C**). Contact dermatitis and local infections (mycotic, viral) were reported as adverse events.^{30,39}

Crisaborole, a non-steroidal topical agent used in cases of atopic dermatitis showed promising results in treating genital psoriasis in a 2020 double-blinded, randomized, vehicle-controlled study.⁴⁰

Dapsone is reported to be effective in vulval pustular psoriasis (100 mg/day, 1 month) in combination with topical treatment.⁴¹

Pregnancy and Breast-feeding

Emollients are considered safe during pregnancy and lactation.²⁶ Pregnant and breastfeeding mothers were excluded from the above clinical studies involving topical corticosteroids and vitamin D analogues. There is no information on medication excretion in breast milk. Topical calcineurin inhibitors are not licensed in pregnancy and in breastfeeding mothers. Topical coal tar usage for short periods of time during pregnancy is considered to only have a small risk.^{26,42} In the case of ustekinumab, secukinumab, ixekizumab and guselkumab, it is recommended to avoid treatment during pregnancy. Decision to use those biologic agents during breastfeeding should be based on a risk/benefit analysis for the child and the mother.⁴³

Follow-up

Active disease should be assessed as clinically required. Stable disease should be reviewed after 1–3 months.

Lichen simplex chronicus

Anogenital lichen simplex chronicus is a common condition. However, the incidence and prevalence have not been established properly. It is estimated to occur in approximately 0.5% of the Western European and American population.⁵ In vulval clinics, it may comprise 10–35% of patients seen.⁵ The condition usually develops in mid- to late-adult life.⁵

Aetiology

Anogenital lichen simplex chronicus is most often encountered in persons with an atopic diathesis: up to 75% of patients have a personal or immediate family history of atopy⁵

- Primary or idiopathic lichen simplex chronicus develops on a background of normal vulval skin, usually in atopics
- Secondary lichen simplex chronicus is superimposed on itchy vulval dermatoses, such as eczema, psoriasis, lichen sclerosis or a fungal or yeast infection.¹³

The condition is triggered by psychological distress, such as anxiety, depression and obsessive-compulsive disorder, and local environmental factors, such as heat, sweating, dryness of the skin, friction and harsh skincare products. Other predisposing

conditions are those which cause generalized pruritis for example uraemia, liver disease and thyroid disease. Although probably rare, it may sometimes be worthwhile to consider neuropathic itch as a possible cause. This could be associated with sacral spinal compression, postherpetic neuralgia and diabetic neuropathy.⁴⁴ Epidermal hyperinnervation seems to have an important role in persistent itching.⁴⁵

Symptoms

- Chronic or intermittent severe pruritus, usually occurring in the evening or during sleep
- Burning and soreness, in case of vulval erosions or ulcers
- Dyspareunia, in case of vulval erosions or ulcers.

Signs

- Poorly demarcated, lichenified plaques, maybe more marked on the side opposite to the dominant hand; skin may feel leathery
- Erosions, ulcers, fissures
- Hyper-, hypo- or depigmented skin areas
- Broken hair in areas of scratching and rubbing.

Complications

- Secondary infection of vulval skin lesions
- Chronic, deep scratching and gouging may lead to severe and irreversible architectural damage⁵
- Vulval lichen simplex chronicus does *not* seem to be associated with a higher risk of squamous cell cancer⁴⁴

Diagnosis

History taking

- Indications of atopic disease in patient or first-degree relatives?
- Skin problems elsewhere? If so, has a diagnosis been made?

Clinical examination is usually sufficient to make a diagnosis. The presence of skin disease elsewhere may be helpful in establishing a differential diagnosis.

Investigation

- Biopsy: seldom necessary. Only in case of uncertainty about the diagnosis. It may be difficult to distinguish lichen simplex chronicus from psoriasis on histopathological grounds
- Screening for infection if indicated (e.g. *Staphylococcus aureus*, *Candida albicans*)
- Dermatological referral for patch testing if contact allergy is suspected^{3,8,9}
- Serum ferritin³: in case of suspicion of low iron store, for example in women who are vegetarian, regular blood donors or have menorrhagia.

Management

Recommended regimens

- Improvement of skin barrier function (saline soaks, followed and later replaced by lubricants – any unperfumed cream will do. Petroleum-based lubricants are too greasy and not recommended)⁵
- Identifying any underlying disease
- In severe disease, superpotent topical corticosteroid, for example clobetasol propionate 0.05% ointment, once or twice daily, with slow tapering if condition improves. In milder cases, fluticasone propionate 0.005% or mometasone furoate 0.1% ointment, once or twice daily, can be prescribed. These steroids should also be tapered as soon as improvement occurs.
- If the plaques of lichen simplex chronicus are very thick, an intralesional injection with triamcinolone could be given.⁴⁶
- Intermittent ice application can be beneficial. Patients should be cautioned to apply ice for a maximum of 15 min to avoid cold injury.⁴⁶
- In case of night-time scratching: sedative antihistamine (e.g. hydroxyzine), or tricyclic antidepressant (e.g. amitriptyline).^{5,47}

Alternative regimens

- Topical calcineurin inhibitors twice daily for up to 12 weeks (pimecrolimus 1% cream, tacrolimus 0.1% ointment) may be used as unlicensed, second-line treatment⁴⁸
- Narrow band ultraviolet B, delivered by comb-like instrument⁴⁹
- Excimer 308-nm laser⁵⁰ – the effect of this treatment may be explained by a reduction of cellular DNA damage and the decrease in epidermal hyperinnervation.
- High-intensity focused ultrasound⁵¹
- Silk fabric underwear may reduce the need for topical steroids⁵²

Follow-up

- Mild disease: as clinically required
- Severe disease (i.e. when using potent topical corticosteroids): 4 weeks, then as required.

Lichen sclerosis

Lichen sclerosis (LS) is an inflammatory skin disease that involves the anogenital area more often than other cutaneous sites; typically it does not affect the vagina and very rarely involves the oral mucosa. It is mainly seen in adult women, but children may be affected. LS is probably underdiagnosed; a recent study determined an incidence of LS in women by age 80

of 1.6%.⁵³ In females, the course is usually chronic, but the condition should be diagnosed as soon as possible, as early treatment prevents scarring and possibly malignant change. Asymptomatic LS needs to be treated to prevent scarring. Spontaneous remission can be observed.

Aetiology

LS is an inflammatory dermatosis of unknown aetiology. A genetic predisposition is implicated. A positive family history is observed in about 10% of patients with vulval LS; however, the prevalence may be higher.⁵⁴ An increased incidence of autoantibodies to the extracellular matrix protein 1 and autoantibodies to BP180 antigen are reported. Their significance is not known but may support the idea of LS being a (humoral) autoimmune disease.^{55,56} Oxidative DNA damage was detected throughout LS biopsies, indicating that oxidative damage to lipids, DNA and proteins may contribute to sclerosis, autoimmunity and carcinogenesis in LS. The possible role of TP53 mutations in the development of vulval cancer in LS is postulated. There are potential triggers for LS, this involves mechanical irritation like tight clothes or bicycle saddles (Koebnerization) and exposure to urine, including urine incontinence.

Symptoms

- Itch (mainly in genital LS in females)
- Soreness
- Dyspareunia or apareunia
- Urinary symptoms (pain, poor urinary stream)
- Other symptoms, for example constipation, can occur if there is perianal involvement, particularly in children
- Can be asymptomatic

Signs

- Pale, white hypertrophic or atrophic areas (vulva, perianal, extragenital)
- Hyperkeratosis
- Sclerosis
- Slight erythema (redness)
- Purpura (ecchymosis) is common in genital LS
- Fissuring anogenitally
- Erosions, but blistering is very rare
- Changes may be localised to the vulva or in a 'figure-of-eight' distribution, including the perianal area
- Scarring may lead to loss of architecture (resorption of the labia minora, fusing in the midline with burying, but not loss of the clitoris)
- Follicular plugging (in extragenital LS)

Complications

- Loss of self-esteem (e.g. concern about the clitoral appearance)

- Development of ano-genital squamous cell carcinoma (actual risk <5%)⁵⁷
- Development of clitoral pseudo-cyst
- Sexual dysfunction
- Urinary dysfunction
- Dysaesthesia

Diagnosis

Characteristic clinical appearance. In typical cases, a biopsy may not be needed, but many clinicians prefer to take a biopsy at presentation. A biopsy should be performed if the clinical diagnosis is uncertain, dysplasia/carcinoma is suspected or there is failure of first line treatment. (**GRADE 1, A**). Clinical and histopathological correlation is essential. In early disease histology can be non-specific.

Key histopathological features (biopsy has to be taken from a typical lesion)⁵⁸:

- Hyperkeratosis
- Atrophic epidermis
- Basal hydropic degeneration +/- pigmentary incontinence
- Lymphohistiocytic infiltrate in hyaline band with loss of elastic tissue in upper dermis
- Follicular plugging in hair bearing skin

Further investigations

Investigation for autoimmune disease if clinically indicated, because some diseases (e.g. thyroid disease, pernicious anaemia, vitiligo, diabetes mellitus) are associated with LS in females.^{56,59,60} These conditions may be asymptomatic. Skin swabs for bacterial, fungal or viral infection are only useful to exclude co-existing infection, if there are symptoms or signs suggestive of this. Patch testing: rarely required and only if secondary (medicament) allergy is suspected. The advice of a dermatologist should be sought.

Management

General advice Patients should be informed about the condition and given written information. Patients should be made aware of the small risk of neoplastic change; however, well-controlled LS may not have an increased risk.⁶¹ They should be advised to contact the doctor if they notice a change in appearance or texture (e.g. lump, ulceration or hardening of skin), or if there is a major change in symptoms.

Patients should be instructed to use emollients and avoid any irritation of the genital skin (cleansing products, frequent exposure to water, incontinence, cloths, some may find that sports such as cycling/horse riding may exacerbate their symptoms). Emollients may give symptom relief after initial steroid treatment.⁶²

Specific treatment Ultra -potent^{63,64} or potent topical steroids⁶⁵ e.g. clobetasol propionate or mometasone furoate are first line recommendations for genital LS (**GRADE 1, A**).

Recommended regimen Various regimens are used; one of the most common being daily use of potent to ultra-potent topical steroids (usually once daily) for three months. Others use the steroid daily for one month, then alternate days for one month and twice weekly for one month (this may be preferred in children to avoid skin atrophy) with review at 3 months. Twice daily application may occasionally be of additional benefit in resistant LS.

Maintenance treatment Proactive maintenance therapy with twice-weekly application of for example mometasone furoate 0.1% ointment or clobetasol propionate 0.05% ointment is effective and safe in maintaining remission, and may help to prevent malignant change.^{61,66} Thirty grams of an ultra-potent steroid should last at least 3 months (**GRADE 1, A**).

Treatment of superinfection An ultra-potent or potent topical steroid preparation combined with antibacterial and antifungal agents for example gentamycin or fucidic acid and nystatin or azole antifungals or an alternative preparation that combats secondary infection may be appropriate if secondary infection is a concern. These should only be used for a short period of time to clear infection.

Allergies to topical preparations Allergies to any compound (also steroids) of a topical preparation may occur after long-term use. In case of a waning effect of a previously good treatment, allergy testing may be indicated.

Alternative second line treatments Topical calcineurin inhibitors are not licensed for the treatment of LS. However, the efficacy of topical tacrolimus 0.1% in the treatment of vulval LS has been confirmed in a comparative randomised study.⁶⁷ There was a more rapid response in the clobetasol propionate 0.05% group, but both treatments were effective after 12 weeks daily application. Significantly, fewer women still had LS in the clobetasol propionate group. Topical tacrolimus 0.1% has also shown to be effective when used for 16 to 24 weeks in males and females with genital and extragenital LS.⁶⁸ This study showed that 77% of evaluable patients responded to treatment with 43% showing a complete response (absence of symptoms and skin findings, excepting induration and atrophy) at 24 weeks. The follow-up period was 18 months and no patient was shown to have skin malignancy or dysplastic change.

Topical tacrolimus 0.03% ointment appears to be an effective treatment for children (probably mainly in girls) with anogenital LS and as maintenance treatment (twice a week), possibly reducing recurrences.⁶⁹

Comparing pimecrolimus 1% cream and clobetasol propionate 0.05% cream, both treatments showed improvement in pruritus and burning/pain after 12 weeks in vulval LS, but clobetasol was found to be superior in improving inflammation.⁷⁰ Another study of pimecrolimus showed that 42% of patients were in 'complete remission' after 6 months application.⁶⁸ Local irritation was the most common side effect with both tacrolimus and pimecrolimus but usually improved after the initial period of use.^{71,72} The long-term risks need to be studied in view of concerns about the possibility of topical immunosuppression increasing risk of malignancy.⁷³

There is some data from two small RCTs of not very high quality showing the efficacy of systemic retinoids for example acicretin in the treatment of genital LS.⁷⁴⁻⁷⁶ Retinoids may be considered if standard therapy for LS has failed but should only be given by a dermatologist, experienced in the use of these agents. They are severely teratogenic and pregnancy must be avoided for at least 2 years after finishing treatment.

Phototherapy is effective in some LS patients. Among different UV regimens, the best data are available for UVA1 and may be considered if topical corticosteroids have failed.^{77,78} However, the well-documented development of carcinomas after PUVA and UVB gives cause for concern, in particular at the genital site.^{77,78}

Lasers of various modalities became popular for the treatment of LS in recent years. However, a systematic review concluded that there is no high quality evidence to support the use of laser for the treatment of LS in males or females. Long-term data of laser are lacking including its adverse effects.⁷⁹

Surgery in vulval LS should only be used for the treatment of coexistent VIN/SCC or fusion.⁸⁰ Disease tends to recur around the scar in females.

Adipose-Derived Stem Cells (ADSC) and Platelet-Rich Plasma (PRP) for the treatment of LS is a further approach to treat treatment-resistant LS. However, current evidence is weak for ADSC and/or PRP. Therefore, as treatment for vulvar LS, this treatment can currently not be recommended.⁸¹

Clitoral LS Lichen sclerosus may appear isolated at the clitoral hood; however, often other vulval parts are also affected. The glans clitoridis is partly covered by the clitoral hood (prepuce), which is a fold of skin that surrounds, protects and lubricates the glans. The prepuce should be easily retractable. The clitoris has got a double innervation and is the female's most erogenous zone. Early signs of clitoral LS are swelling of the prepuce; white plaques, fissures, fusion and scarring may follow. Clitoral involvement should be searched for and treated like LS at other genital sites. Mechanical triggers are supposed to be important in maintaining LS, such as wearing tight clothing and should be avoided. Topical preparations should be massaged in gently. Surgery, to treat fusion is only indicated in rare situations (e.g. severe problems with self-esteem, sexual function or urination).

There is a chance of recurrence after surgery because the inflammatory process may not have ceased. Surgery should only be performed by an experienced surgeon and after careful counselling about the intervention, adverse effects and potential recurrences.

Extragenital LS There are fewer studies for the treatment of extragenital LS. UVA1 phototherapy is a potential first-line treatment option.^{77,78} Potent topical steroids and topical calcipotriol, possibly under occlusion, may be tried in extragenital LS.⁸²

Pregnancy and breast-feeding

Lichen sclerosus usually takes a favourable course during pregnancy and LS is no contraindication for vaginal delivery.⁸³ However if needed:

- Limited amounts of potent topical steroids are safe to use while pregnant or breast-feeding.
- Topical calcineurin inhibitors are contra-indicated whilst pregnant or breast-feeding.
- Retinoids are absolutely contra-indicated during pregnancy and for at least 2 years before conception. They should be used with caution in females of child-bearing age.

Onward referral criteria

Those with active disease which has not responded adequately to treatment should be referred to a physician specialized in the condition. Any patient who develops differentiated or undifferentiated VIN or an SCC on a background of LS should be seen and followed up by an experienced specialist.

Follow-up

- After 3 months to assess response to treatment
- Stable disease should be reviewed annually and this can be done by the GP in those with well-controlled disease. This must be communicated to the patient and GP by the specialist.
- Patients should be informed that if they notice the development of a lump, sore area, change in symptoms or change in appearance they should seek prompt medical review.

Research initiatives are on-going to prioritize research questions and standardise outcomes for clinical trials.^{84,85}

Lichen planus

Aetiology

Lichen planus (LP) is an inflammatory disorder with manifestations in skin, hair, nails and genital and oral mucous membranes; more rarely it affects the lacrimal duct, oesophagus and external auditory meatus. Although the exact pathogenesis is

unknown, it probably represents an immunological response by T-cells activated by, as yet unidentified antigens. Weak circulating basement membrane zone antibodies have been demonstrated in 61% of 56 patients with biopsy-proven erosive LP of the vulva but are of unknown significance.⁸⁶ In some cases, there is overlap between LP and LS⁸⁷ and the two conditions may coexist.⁸⁸ Vulval LP is not rare and in a recent review was the diagnosis in 8.8% of patients attending a dermatology clinic in a tertiary hospital.⁸⁹

Symptoms

- Itch/irritation
- Soreness
- Dyspareunia
- Urinary symptoms
- Vaginal discharge
- Can be asymptomatic.

Signs

The anogenital lesions of LP may be divided into three main groups according to their clinical presentation:

Classical Typical papules occur on the keratinized anogenital skin, with or without Wickham's striae, on the inner aspect of the vulva. Hyperpigmentation frequently follows their resolution, particularly in those with dark skin. This type of LP may be asymptomatic. Vulval lesions were found in 19 out of 37 women with cutaneous LP, with four of the 19 having had no symptoms.⁹⁰

Hypertrophic These lesions are relatively rare and can be difficult to diagnose. They particularly affect the perineum and perianal area, presenting as thickened warty plaques which may become ulcerated, infected and painful. The clinical appearance may mimic malignancy. They are not usually accompanied by vaginal lesions.

Erosive This is the most common subtype to cause vulval symptoms. The mean age of onset of vulval symptoms in 114 women with erosive LP was 56.9 years.⁹¹ The mucosal surfaces are eroded. At the edges of the erosions, the epithelium is red-to-purple coloured and a pale network of Wickham's striae is sometimes seen. It is important to recognize vaginal involvement in erosive LP (which can occur in isolation) and start treatment early, as it can lead to scarring and complete stenosis. The lesions consist of friable telangiectasias with patchy erythema which are responsible for the common symptoms of dyspareunia, postcoital bleeding and a variable discharge, which is often serosanguinous. As erosions heal, synechiae and scarring can develop.⁹² This type is also seen in the oral mucosa although at this location synechiae are uncommon. The term vulvo-vaginal-gingival

syndrome is used when erosive disease occurs in these three sites. The presenting symptoms are usually pain and soreness in the affected area.

Diagnostic criteria

Diagnostic criteria for vulval erosive LP were proposed in an international e-Delphi exercise.⁹³ It was suggested that at least three of the following criteria should be present to make the diagnosis: (i) well-demarcated erosions/erythematous areas at the vaginal introitus; (ii) presence of a hyperkeratotic border to lesions and/or Wickham striae in surrounding skin; (iii) symptoms of pain/burning; (iv) scarring/loss of normal architecture; (v) presence of vaginal inflammation; (vi) involvement of other mucosal surfaces; (vii) presence of a well-defined inflammatory band involving the dermo-epidermal junction; (viii) presence of an inflammatory band consisting predominantly of lymphocytes; and (ix) signs of basal layer degeneration.

A recent study⁹⁴ of 243 women with clinically suspected vulval LP with available histopathology, 50 patients with biopsy-proven vulvar LS and 50 patients with culture-proven chronic vulvovaginal candidiasis concluded that clinical features that significantly differentiated the conditions were the presence of erosions, glazed erythema, oral involvement, pain/burning sensation and a hyperkeratotic border. A score ≥ 2 correlated with a histopathological diagnosis of vulvar LP, with a sensitivity of 100% and a specificity of 92% and 88% when compared against vulvar LS and chronic vulvovaginal candidiasis, respectively.

Involvement of the vagina practically excludes lichen sclerosus, which typically spares non-keratinized mucosal surfaces. Skin changes elsewhere can be helpful but overlap between LP and LS is described. Immunobullous disorders such as cicatricial mucous membrane pemphigoid and pemphigus can clinically resemble erosive LP.

Dermoscopy: specific dermoscopic features that may aid clinical diagnosis of LP include the presence of thick linear irregular vessels arranged diffusely throughout lesions, peripheral Wickham's striae and an intense red background.⁹⁵

Histology of vulval biopsy: features of classical LP include irregular 'saw-tooth' acanthosis, increased granular layer, basal cell liquefaction and a band-like dermal mainly lymphocytic infiltrate.⁵⁸ However histology may be non-specific.

Erosive mucosal LP is characterized by prominent epithelial apoptosis and a lymphocytic inflammatory infiltrate, the presence of plasma cells and epidermal ulceration with more typical changes of LP at the margins of the ulcer.⁹⁶ In erosive LP of the vulva, there is widespread disruption in several basement membrane zone components, including hemidesmosomes and anchoring fibrils.⁹⁷

Vulvar LP on keratinized skin has a diversity of appearances and presents a particular challenge.⁹⁸ At this site, the presence of

basal layer degeneration is the single most helpful feature to distinguish LP from nodular prurigo and lichenified psoriasis, but this may be masked or mimicked by inflammation relating to superinfection. Pseudo-epitheliomatous hyperplasia may be confused for microinvasive squamous cell carcinoma, and granulomatous infiltrates may be misinterpreted as systemic autoimmune or infectious diseases.⁹⁵

Further investigations

- Biopsy is indicated if the diagnosis is uncertain clinically or coexistent intraepithelial neoplasia/squamous cell carcinoma (SCC) is suspected. Direct immunofluorescence should be performed if an immunobullous disease is considered in the differential diagnosis. Only 25% are classic on biopsy and clinico-pathological correlation is important.
- Thyroid and other autoimmune disease is only rarely associated with vulval LP. Investigation for autoimmune disease is indicated if there is clinical suspicion of abnormality.⁹⁹
- Skin swab: to exclude secondary infection, especially of excoriated lesions.
- Patch testing: if medicament contact allergy suspected.

Whilst a link with hepatitis C and sometimes B has been noted in some (especially Mediterranean) countries, a UK study of 100 women with vulval mucosal LP found no evidence of increased incidence and concluded that routine screening is unnecessary.¹⁰⁰ Nevertheless screening may still be prudent in populations with a high prevalence of viral hepatitis.

Complications

- Scarring, including vaginal synechiae, particularly seen in erosive disease
- Development of SCC. In the only available prospective study, which comprised of 114 patients with vulvar LP followed for a mean of six years, seven patients developed vulval intraepithelial neoplasia and two (1.8%) developed anogenital SCC.¹⁰¹ Patients with LP-associated SCC have been reported to have a high rate of inguinal metastases, recurrent vulvar cancers in diseased mucosa and disease-related death.¹⁰² On the other hand, a clinicohistopathologic review⁸⁸ of 43 consecutive vulvectomies and wide local excisions for HPV-independent vulvar SCC over an 11-year period found no evidence of LP in any of the cases and all were considered to have underlying LS. Authors concluded that vulvar SCC associated with LP is rare, but emphasized that differentiated vulvar intraepithelial neoplasia may superficially resemble erosive or hypertrophic LP. Although it would appear logical to aim for effective disease control in vulval LP, it is not known whether early treatment, effective control or long-term maintenance treatment lessens the risk of malignancy.⁹¹

Management

General advice Vulval LP, particularly erosive disease, may have a major negative impact on quality of life and sexual function of affected patients.¹⁰³ Patients should be adequately informed about their condition and given written information. They should be made aware of the small long-term risk of neoplastic change and advised to seek urgent medical advice if they notice a change in appearance or texture (e.g. lump, hardening of skin or persistent ulceration).

Treatment There are two randomized controlled trials providing evidence to guide treatment of vulval erosive LP.^{104,105}

Topical treatment. *Recommended Regimen*

- Ultrapotent topical steroids for example clobetasol propionate. (**GRADE 2, B**). In a study of 114 patients in a vulval clinic, 89 used ultrapotent topical steroids as first-line treatment of whom 75% improved and 54% were symptom-free. However, in only 9% was there resolution of signs of inflammation.⁹¹ There is no evidence on the optimal regimen.
- Maintenance treatment may be required and can either be with weaker steroid preparations or less frequent use of potent steroids.
- Vaginal corticosteroids: Delivery of corticosteroids to the vagina is not easy: the application of corticosteroid ointment on a tampon overnight may be helpful. A proprietary preparation containing hydrocortisone rectal foam introduced into the vagina with an applicator, 1–2 times daily may be useful. Prednisolone suppositories may be used in more severe cases

Alternative Regimens

- The topical calcineurin inhibitors pimecrolimus and tacrolimus may be effective in vulval LP; pimecrolimus may be better tolerated.¹⁰⁶ In a retrospective series of 16 women with vulval LP, topical tacrolimus effectively controlled symptoms and improved lesions in all but one patient. The effect may be temporary, requiring continued use of tacrolimus, which however appears to be safe and effective in controlling disease activity.¹⁰⁷

Systemic treatments

There is no consensus and little evidence base for the use of systemic agents. In the vulvo–vaginal–gingival syndrome there is general agreement that azathioprine, dapsone, griseofulvin and minocycline, all tried empirically, are of little or no benefit. Of the limited evidence available, the most favourable in terms of efficacy appears to be for hydroxychloroquine, methotrexate (MTX) and mycophenolate mofetil given in standard doses.

- A recent retrospective study¹⁰⁸ reported that 9 of 15 patients (60%) responded to hydroxychloroquine, with almost half experiencing long-term effect.
- Another study¹⁰⁹ reported significant improvement in 19 of 27 patients (70%) with erosive LP treated with long-term MTX however other studies^{91,110} reported poorer results.
- Mycophenolate mofetil^{111,112} and cyclosporin¹¹³ may also be effective and worth considering for selected cases.
- Oral steroids, for example prednisolone 40 mg/day, tapered off over a few weeks, may be used for severe flares; courses can be repeated as necessary.

The retinoid acitretin can be helpful in hypertrophic disease. The drug is severely teratogenic and is absolutely contraindicated during pregnancy. Pregnancy must be avoided for 2 years after finishing treatment. It should be used with caution in other females of child-bearing age.

A well-planned multicentre, four-arm, assessor-blind, randomized, controlled trial in patients with vulval erosive LP, with an internal pilot phase designed to provide high-quality evidence, comparing hydroxychloroquine, methotrexate, mycophenolate mofetil and prednisolone, given in addition to standard topical therapy unfortunately closed without reaching its recruitment target.^{111–114} Treatment ‘success’ only occurred in the hydroxychloroquine (2/6 patients, 33%) and mycophenolate mofetil (2/5 patients, 40%) groups. Nevertheless lessons learnt from this trial, specifically with regard to study methodology, may help guide further research in this condition.¹¹⁵

Biological agents have shown varying results. However, the rising trend of TNF- α inhibitors inducing LP-like eruptions including erosive oral and vulval disease^{116–118} reserves these drugs for only the most recalcitrant cases. The anti-IL-2 receptor antibody basiliximab was reported to be effective in a single case of severe erosive oral LP, although its use has not been evaluated in vulval disease.¹¹⁹

All these potentially toxic therapies need careful monitoring and are best supervised by a dermatologist in the context of a specialized clinic.

Surgery

Surgery may be necessary for management of symptomatic vulval and vaginal adhesions and scarring, but is contraindicated in patients with active, inflammatory disease.¹²⁰ In a study of 11 women with LP scarring,¹²¹ surgical lysis of vulvo–vaginal adhesions allowed intercourse in 55% and decreased urination difficulties in 75%, of the patients, 91% stated they were happy with the surgery and would recommend it to others. However, sexual difficulties may persist even after surgery.¹²¹ Potent topical steroids should be used routinely immediately after surgical adhesiolysis in vulvo–vaginal LP as they have been shown to improve long-term outcomes and function.¹²²

A novel approach is focused ultrasound therapy for which a positive response was reported in 127 of 135 patients with non-

neoplastic epithelial disorders of the vulva, including all seven patients with vulval LP, in a prospective study.¹²³

Pregnancy and Breast-feeding

- Topical steroids are safe to use while pregnant or breast-feeding.
- Topical calcineurin inhibitors are not licensed whilst pregnant or breast-feeding.
- Retinoids are absolutely contra-indicated during pregnancy and for at least 2 years before conception. They should be used with caution in females of child-bearing age.

Onward referral

Referral to a multidisciplinary vulval clinic is recommended for erosive disease, recalcitrant cases or those in whom systemic therapy is considered.

Follow-up

- At 2–3 months to assess response to treatment.
- Active disease should be assessed as clinically required. Erosive vulval LP needs long-term specialized follow-up.
- Stable disease should be reviewed annually, except in well-counselled patients who control their symptoms well. If review is to be undertaken by the GP, this should be communicated to the patient and GP by the clinic.
- Patients should be advised to seek urgent medical advice if they notice a change in appearance or texture (e.g. lump, hardening of skin or persistent ulceration).

Vulvodynia

Vulvodynia is defined as ‘vulvar pain of at least 3 months’ duration, without a clear identifiable cause, which may have potential associated factors’.¹²¹ It is categorized as generalized or localized, and provoked, unprovoked or mixed (both provoked and unprovoked; see symptoms). According to the last version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), vulvodynia can be considered as a female genito-pelvic pain/penetration disorder.^{122–125}

Aetiology

Vulvodynia is currently considered as a dysfunctional sensory processing involving both the peripheral and the central nervous system.^{126–128} This dysfunction is similarly observed in other chronic painful conditions such as fibromyalgia, interstitial cystitis/painful bladder, irritable bowel syndrome and temporomandibular joint dysfunction. These are all significantly associated with vulvodynia.^{129–132} A genetic predisposition to both vulvodynia and these chronic pain conditions is suspected.¹³³ Triggering or maintaining factors have been identified, which are mainly pelvic floor muscle dysfunction^{134–136} and psychosexual disturbances either those that are pre-existing or resulting from the chronic pain.^{137,138}

The role of candidiasis,^{139,140} and hormonal contraception as trigger factors are not fully established.¹⁴¹ Women with vulvodynia are more likely to report childhood sexual abuse and severe physical abuse than women without vulvodynia.^{142,143}

Clinical features

Symptoms

The mnemonic OPQRST can be used to describe the vulvar discomfort

O - Onset

An initiating event, either physical (infection, dermatosis, surgical procedure in the pelvic area) or emotional, is frequently found at the onset of vulvodynia. The role of candidiasis as a trigger of vulvodynia is debated because this infection is mostly self-reported.¹⁴⁰

P - Provocation

The discomfort may be either provoked or unprovoked or mixed.

❖ Provoked

- By sexual contact: penetration (introital dyspareunia) or touch.
 - Introital dyspareunia may be either primary (since the first intercourse) or secondary (occurring after a period of painless intercourse).
- By non-sexual contact such as tampon insertion, tight clothing, sitting position or gynaecological examination.

❖ Unprovoked

- The discomfort is not triggered by touch. It occurs spontaneously.

❖ Mixed

- The discomfort is both spontaneous and aggravated by local contacts either sexual or non-sexual.

Q - Quality

Burning is the main symptom but many other uncomfortable sensations are reported (tingling, stinging, rawness, irritation, etc.). Itch may be present.

R - Region

The discomfort may be either localized or generalized

❖ Generalized

- The whole vulva is involved (clitoris, labia minora and majora, vestibule). The patient may also describe the symptoms spreading to the thighs and perianal area.

❖ Localized

- The most frequently involved site is the vestibule (i.e. the introitus), particularly its posterior aspect. This is termed vestibulodynia. Provoked vestibulodynia is the best reproducible subset of vulvodynia. More rarely, the discomfort is localized to other parts of the vulva: labia minora or majora, clitoris (clitorodynia).

S – Severity

The severity of the discomfort is highly variable from one day to another in an individual patient and from one patient to another. Vulvodynia diversely impacts intimacy and sexual communication and usually provokes anxiety and depression. Partner response to sexual pain, degree of pain catastrophizing and self-efficacy are also highly variable.¹⁴⁴

T – Time

Vulvodynia is a chronic pain condition having usually lasted months or years before the diagnosis is made. Significant improvement or complete remission may occur, spontaneously or following treatment.^{145–147}

Signs Inspection of the vulva reveals no relevant physical findings which means that the vulva has a normal appearance or that, if a lesion is found, this lesion cannot explain the discomfort (example: a wart cannot explain diffuse burning; LS usually explains itch and not pain).

In provoked vestibulodynia a gentle pressure on the vestibule by a cotton tipped applicator elicits tenderness or pain. Neurological examination is normal: in particular, there is no objective neurological findings).

Complications Vulvodynia may have a significant impact on psychological and sexual well-being, which may require specific interventions.¹⁴⁴

Diagnosis Vulvodynia is a clinical diagnosis based on history and physical examination, which excludes any other cause of vulvar discomfort.

Differential diagnosis

Neurological conditions responsible for perineal pain such as pudendal neuralgia should be suspected in the case of unilateral or diffuse vulvar pain, associated sphincter disturbances and of objective neurological abnormalities. Complementary investigations such as imaging (pelvic and lumbosacral MRI to exclude a compressive process) and nerve blocks help to assess the diagnosis.¹⁴⁸

Management

Information Patients should be given a full explanation of their condition both verbal and in writing.

- Name the condition (vulvodynia)
- Do not cast doubt about the reality of the pain (not “in the head”) and acknowledge its significant impact on all aspects of the quality of life.
- Explain the current knowledge about mechanisms, contributing factors, treatment and prognosis.

Multidimensional approach As for any chronic pain, a multidimensional approach to patients with vulvodynia is widely

recommended.^{149–151} However, levels of evidence are low.^{152–154} In addition, placebo effect is strong for vulvodynia as well as for female sexual dysfunction.^{155,156}

Vulval care measures

- Avoidance of irritating factors
- Use of emulsifying ointments and soap substitutes.

Pain targeted treatments

❖ Topical pain modifiers (GRADE 2)

- Local anaesthetics for example 5% lidocaine ointment or 2% lidocaine gel are mainly prescribed in patients with introital dyspareunia resulting from provoked vestibulodynia. Lidocaine should be applied 10–20 min prior to penetrative sex and washed off just before penetration. Long-term daily use of Lidocaine 5% (12 weeks applications, four times a day) is not more effective than placebo in reducing vestibular pain.¹⁵⁷
- Botulinum neurotoxin (20–50 units) injected in the bulbo-cavernosus muscles is not superior to placebo for reducing pain.^{158–160}
- Further investigations are needed to establish the efficacy of 2% amitriptyline cream alone or associated with baclofen.^{161,162}
- The benefit of 0.025% to 0.05% capsaicin cream is not demonstrated and its use is limited by burning.^{159–164}
- Cannabis: although medical cannabis is considered as a possible effective and safe approach to chronic pain including fibromyalgia^{165,166} and female sexual dysfunction,¹⁶⁷ there is currently not enough evidence to recommend it for vulvodynia.¹⁶⁸

❖ Oral pain modifiers (GRADE 2)

- Antidepressants
 - Tricyclic antidepressants: although, largely used to treat vulvodynia (particularly generalized unprovoked) there is insufficient data to support their benefit.¹⁶⁹
 - **Amitriptyline**, a tricyclic antidepressant is the most frequently used. As opposed to the results of uncontrolled studies,¹⁷⁰ two small RCT studies of low or moderate quality did not confirm efficacy.^{171,172} Low daily doses are usually prescribed (5 to 50 mg; IV) and tolerance is frequently poor.
 - **Desimipramine** used with an increasing dosage (from 25 mg to 150 mg) for 12 weeks, was not superior to placebo.¹⁵⁷
 - Serotonin-norepinephrine reuptake inhibitors:
 - **Oral milnacipran**, 50–200 mg per day for 12 weeks reduced coital pain.¹⁷³
- Antiepileptics
 - Gabapentin (1200 to 3000 mg per day) was not more effective than a placebo to reduce tampon test pain and

dyspareunia¹⁷⁴ but had a positive impact on sexual function, particularly in the arousal domain.¹⁷⁵

- There is little evidence for the use of pregabalin.¹⁷⁶

❖ Energy based interventions

Transcutaneous Electrical Nerve stimulation (TENS)¹⁷⁷ can be self-administered and is best integrated in a multidimensional strategy.¹⁷⁸ So far, there is no evidence of the efficacy of **fractional CO₂ laser therapy, low-level laser therapy and radiofrequency** for treating vulvodynia.^{179–181} There is an FDA warning against the use of energy devices to treat symptoms related to sexual function, menopause, urinary incontinence, because of concerns regarding adverse events. (FDA Safety Communication. Available at: <https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-efforts-safeguard-womens-health-deceptive-health-claims>).

❖ **Acupuncture** alone or associated with lidocaine has shown effectiveness in small clinical trials, both on pain relief and sexual functioning.^{182–184} Improvement of the quality of the study protocols including comparing different acupuncture strategies are on-going.^{185,186}

Hormones There are conflicting data and recommendations regarding cessation of combined hormonal contraception or addition of topical oestrogen alone or in combination with testosterone.^{144,187}

Physical therapy^{188,189} (GRADE 1,B) Physical therapy is considered as a first line treatment of vulvodynia. It aims to rehabilitate the pelvic floor musculature by enhancing muscle proprioception, relaxation, discrimination and elasticity, normalizing muscle tone, desensitizing the painful vulvar tissue. It includes education addressing at best both anatomy and sexual functioning and pelvic floor exercises with biofeedback, manual therapy and dilation (in isolation or association). Best results are obtained with physiotherapists experienced in the management of chronic vulvar pain and its sexual impact.

Psychosexual interventions (GRADE 1,B) Psychosocial interventions include cognitive-behavioural therapy (CBT), pain management, sex therapy and psychoeducation, offered either

alone or in combination. These interventions aim not only to reduce pain but also to improve women and partners' sexual function, sexual well-being and relationship satisfaction by targeting the thoughts, emotions, behaviours and couple interactions associated with vulvodynia.¹⁴⁴

- **CBT** was shown to improve pain during intercourse as much as vestibulectomy¹⁹⁰ and was superior to topical corticosteroids and supportive psychotherapy in terms of reduction of pain and improvement of sexual functioning.^{191,192}
- **Couple based CBT** approach seems to be appropriate as vulvodynia has a psychological and behavioural impact both on the patient and her romantic partner.¹⁹³
- **Mindfulness** is increasingly used alongside or instead of CBT for chronic pain disorders including vulvodynia.¹⁸⁸ Mindfulness-based cognitive therapy (MBCT) was superior to CBT in terms of reduction of pain at intercourse and equal to CBT for the other pain and sexual related outcomes.^{194–196} Women who present with high credibility about mindfulness, in shorter relationships and with secondary PVD might respond better to MBCT than to CBT.¹⁹⁷

Lifestyle advice Lifestyle factors such as physical inactivity, stress, poor sleep, unhealthy diet and smoking are associated with chronic pain severity and sustainment, and lifestyle changes have a positive impact on chronic pain.¹⁹⁸ Although there is no specific evidence of these data and benefits in women with vulvodynia, lifestyle advice could be part of the multidimensional approach.¹⁵¹

Surgery Surgery is usually not recommended for chronic pain related to a dysfunction in pain processing (such as vulvodynia). However, despite a low level of evidence,^{144,199} vestibulectomy (posterior or total, with or without vaginal advancement) is currently considered as a 'last resort' intervention for provoked vestibulodynia, after failure of all the available therapeutical options.^{200,201} According to the published data, vestibulectomy durably reduces introital dyspareunia and patients are satisfied with the results.^{202–204} Results on sexual function however are moderate²⁰² or not superior to electromyographic biofeedback or behavioural cognitive therapy.²⁰⁵ Short and long-term

Table 1 Evolution of the International Society for the Study of Vulvovaginal Disease terminology

| Friedrich (1976) ²⁰⁹ | Wilkinson <i>et al.</i> (1986) ²¹⁰ | Sideri <i>et al.</i> (2004) ²¹¹ | Bornstein <i>et al.</i> (2016) ²⁰⁸ |
|-----------------------------------|---|--|---|
| Vulval atypia | VIN 1 | Flat condyloma or HPV effect | LSIL |
| A. without dystrophy | Vin 2cx | VIN, usual type | HSIL |
| B. with dystrophy | | | |
| Squamous carcinoma <i>in situ</i> | VIN 3 | VIN usual type | HSIL |
| | Differentiated VIN | VIN differentiated type | DVIN, differentiated-type VIN |

complications may occur such as bleeding, wound dehiscence, Bartholin's cyst and unsatisfying cosmetic appearance.

Follow-up

- Multidisciplinary long-term follow-up (**GRADE 1,B**)
- Every 3 months until improvement

Health promotion

Health providers should be better educated about the diagnosis and the management of vulvodynia. Delay in diagnosis and inappropriate treatments may have a negative prognostic impact.

Vulval intraepithelial neoplasia (VIN)

Introduction

VIN is a chronic vulval skin disorder characterized by dysplastic changes of the squamous epithelium. It is a premalignant lesion, although spontaneous regression has been reported.²⁰⁶ In the last 100 years, premalignant lesions of the vulva have been described, but there always was a debate about the clinical and pathological characteristics of these lesions. The terminology has changed several times since the first description in 1922: 'dyskeratose erythroplasiiforme de la muqueuse vulvaire'.²⁰⁷ The International Society for the Study of Vulvovaginal Disease (ISSVD) had been leading in the process of choosing new terminology for premalignant vulval lesions. The last version of the terminology was accepted by the ISSVD in 2015 (Table 1):

- Low-grade Squamous Intraepithelial Lesion (SIL) of the vulva or vulval LSIL.
- High-grade SIL of the vulva or vulval HSIL
- Vulval intraepithelial neoplasia, differentiated type²⁰⁸

Aetiology

Using the latest ISSVD terminology, there are two premalignant vulval lesions, which can lead to a squamous cell carcinoma of the vulva, namely HSIL and DVIN. These are completely different entities with respect to aetiology, malignant potential and treatment. HSIL is caused by a persistent infection with high risk Human Papilloma Virus (HPV). The incidence of HSIL is approximately 5 per 100 000 women per year and is increasing,²¹² with the highest peak between 35 and 49 years.²¹³ A reason for the increased incidence may be the increase of anogenital HPV infections and/or a better diagnosis by the more liberal use of vulval biopsy. Risk factors are smoking and an immunocompromised state.

DVIN is associated with LS and LP and has no relation with HPV. DVIN occurs mainly in elderly women, and comprises less than 5% of VIN lesions. The malignant potential of DVIN is higher than that of HSIL.^{214,215} The aetiology of DVIN is not clear.

Symptoms and signs

| | HSIL | DVIN |
|----------|--|--|
| Symptoms | Itching, burning, irritation Pain Psychosexual complaints Asymptomatic | Symptoms are often due to the underlying lichen sclerosus or lichen planus |
| Signs | Clinical appearance is very variable Plaques, whitish, erythematous or pigmented Multifocal | Difficult to distinguish from lichen sclerosus lesions Grey-white or red lesion Roughened surface or ulceration More often unifocal than HSIL |

Complications

HSIL and DVIN

- Development of vulval squamous cell carcinoma
- High rate of recurrence after treatment
- Psychosexual complaints

Diagnosis

HSIL and DVIN is often a multifocal disease. It is important to take a biopsy of all lesions (mapping) (**GRADE 1**).

Investigation

HSIL Biopsy

- Histopathological characteristics: disorganization of squamous epithelium, cytological atypia, high nuclear/cytoplasmic ratio, mitotic figures

DVIN Biopsy: histopathology is difficult

- Histopathological characteristics: hyperplasia, hyperkeratosis, parakeratosis, elongation and anastomosis of rete ridges, basal cell atypia, prominent nucleoli, atypical mitosis in basal layer, dyskeratosis, hypermaturation of rete ridges

Immunohistochemistry (p16 and p53) is helpful in differentiating between HSIL and dVIN. HSIL is HPV driven and DVIN is independent of HPV; p16 is a marker for HPV positivity, so HSIL is p16 positive and DVIN is p16 negative. HSIL shows normal p53 and DVIN shows mutations in the p53 gene.

There are two other precursors of vulvar cancer, they are both HPV independent.

- VAAD: Vulvar acanthosis with altered differentiation²¹⁶
- DEVIL: Differentiated exophytic vulvar intraepithelial lesion²¹⁷

Management

HSIL Surgical treatment has been the first choice of treatment, but recurrence rates are high and there is a negative effect on quality of life and sexual function. A new treatment modality is the application of imiquimod cream, an immune response modifier with indirect antiviral and antitumour properties.²¹⁸ (GRADE 1 B)

- Surgical cold knife excision
- Laser CO2 therapy
- Loop electrosurgical excision procedure (LEEP)
- Imiquimod cream
- Follow up without treatment (spontaneous regression)

DVIN

- Surgical cold knife excision

Follow up

Close follow-up is mandatory, lifelong

HSIL

- Every 6–12 months, with annual cervical smear

DVIN

- Depends on underlying disease, but at least every 6 months

Vaccination

Several types of therapeutic HPV vaccines have been developed showing different rates of clinical success. Today, therapeutic vaccines are not yet available for routine clinical use.

Prophylactic HPV vaccination was introduced in 2007 with the goal of reducing the incidence of cervical (pre)malignancies and to reduce other HPV related lesions like HSIL.²¹⁹ The quadrivalent HPV 6/11/16/18 and bivalent (16/18) vaccine shows prevention against HPV 16- and 18-related high grade lesions of vulva and vagina, in women who were HPV 16 or 18 negative before vaccination.²²⁰ The nonavalent vaccine (HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58) does it slightly better.²²¹

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Data sharing is not applicable to this article as no new data were created or analysed in this study.

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