2016 European guideline for the management of vulval conditions

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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, and a chaperone should be offered in all cases and this offer should be documented clearly in the patient records. The proposed examination should be adequately explained to the patient 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 soundproofed, with a suitable examination couch of adjustable height [1].

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 anticandidal treatment, especially if cultures are negative for candida, then a full genital examination should be undertaken 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 in all patients, either as the cause of the symptoms or developed secondary to the symptoms, and assessed if appropriate.

General advice for all vulval conditions
(see related IUSTI patient information leaflet on http://www.iusti.org/regions/Europe/PatientInformation.htm)

- Avoid contact with soap, shampoo and bubble bath. Simple emollients can be used as a soap substitute and general moisturiser
- Avoid tight fitting garments which may irritate the area
- Avoid use of spermicidally lubricated condoms
- 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 e.g. urine and menstrual blood.

Sexual partners

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

1. 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 [2].

Aetiology

Atopic dermatitis – there is increasing evidence that this is due to a defect in the barrier function of the skin [3]. 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 [4].

Irritant contact dermatitis – this is the commonest type of eczema to affect the vulva. The vulval epithelium is less efficient as a barrier than skin elsewhere [5] and is in contact with moisture, 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 – this is 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 - this is an inflammatory, desquamative dermatosis affecting the scalp, face and more rarely, the trunk. Seborrhoeic dermatitis and psoriasis may be associated and have similar pathology. Yeast organisms on the skin may have a role in the development of seborrhoeic dermatitis in predisposed individuals [6]. This form of dermatitis rarely affects the vulva and does not have specific features. In contrast to vulval psoriasis, no specific clinical features of seborrheic dermatitis are recognized on the vulva and there is debate about whether this condition exists on the vulva. Therefore this diagnosis should be made only after exclusion of all other causes of vulval erythema.

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.
- Excoriations
- Erosions – if acute
- Serous discharge with oozing and crusting, especially if secondary infection is present
- 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 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.

- Streptococcal 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 should be performed if there are atypical features or failure to respond to treatment (IV, C).

Patch testing (III, B) 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. In addition to the standard series of allergens, any patient with a suspected vulval allergic contact dermatitis should be tested to medicaments,

preservatives and specific products used on the vulva, at the appropriate dilutions [7,8]. 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.

Mycological and bacteriological specimens will exclude candidiasis, tinea and bacterial infection.

Management

1. Avoidance of irritants and possible allergens that may be precipitating factors eg. cleansers, fragrances, wet wipes etc. (IV, C) 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 eg. emulsifying ointment. (IV, C).

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 (IV, C).

4. Treat any co-existing infection with a combination steroid/antifungal or steroid/antibacterial (IV, C).

5. A sedating anti-histamine given at night should reduce the damage inflicted by scratching.

Calcineurin inhibitors (IV, C) (topical tacrolimus and pimecrolimus) can be tried for resistant cases, but their use is limited by stinging on application [9].

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.

2. VULVAL PSORIASIS

Aetiology

Psoriasis is an immune-mediated disease with genetic predisposition. Several trigger factors are described (some of them present in populations at risk for STI) [10]: infections (e.g. streptococcal, HIV), smoking, alcohol excess, physical factors (e.g. tattoos, piercing) and medication (e.g. systemic steroids, beta-blockers, lithium, non-steroidal anti-inflammatory drugs).

Clinical features

Genital skin is affected in 29-46% of psoriatic patients [11]. Vulval psoriasis can be present in patients with psoriasis vulgaris as localized disease (2-5% of cases [12]) or in a disseminated form (affecting also 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 herpetiformis 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.

Symptoms

- Vulval itch, pain or burning sensation can be present.

Signs

- Monomorphic, symmetric 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 than in the genitals that other locations. Lesions can extend to adjacent regions (inguinal, perineal, pubic). Sometimes painful fissures can be present [13].

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

Associated disorders

Psoriatic arthritis [14] occurs in 15% - 30% of patients with psoriasis vulgaris or exudative psoriasis. Cardiovascular disease, hypertension, malignancy, diabetes, metabolic syndrome, inflammatory bowel disease or autoimmune diseases can also be associated with psoriasis.

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

Investigation
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 [15].

Investigations for possible associated inflammatory diseases should be considered.

Management
General Advice
The patient should avoid all known trigger factors including scented detergents, synthetic underwear and tight pants [13].
Topical treatment is indicated for localized vulval psoriasis. In patients with disseminated or generalized lesions of psoriasis the systemic therapy is also effective for the genital lesions – this treatment is described in other guidelines [16].
Due to possible local adverse reactions (mainly irritant), it is recommended to avoid the use of anthralin, tazarotene and ultraviolet therapy when treating vulval psoriasis (II, B) [13].

Recommended Regimens
Treatment will reduce the thickness of the lesions, the degree of erythema and remove scales. All therapeutic possibilities should be presented in order 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 [17]. In order to cover the whole genital area 0.5 fingertip-units should be sufficient [18].

1. Topical corticosteroids prescribed in sequential or rotational therapeutic regimens (I, B) [19-21]: mid potency topical steroids followed by low potency topical steroids.

2. Topical vitamin D analogues in mono-therapy or in combination with topical corticosteroids (I, B) [22, 23].

3. Coal-tar preparations (e.g. 1-5% liquor carbonis detergens in aqueous cream) in mono-therapy or in combination with topical corticosteroids (III) [22, 24].

Emollients are recommended to reduce local irritation induced by other topical treatment and to maintain the therapeutic results (I, B) [22,25].

Unlicensed treatments
Topical calcineurin inhibitors (tacrolimus, pimecrolimus) are reported to be effective in vulval psoriasis (III). Contact dermatitis and local infections (mycotic, viral) can be induced [21, 26].

Dapsone is reported to be effective in vulval pustular psoriasis (100 mg/day, one month) in combination with topical treatment (IV) [27].

Pregnancy and Breast-feeding
Emollients are considered safe during pregnancy and lactation [17]. Pregnant and breast-feeding 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 recommended in pregnancy and in breast-feeding mothers. Topical coal tar usage for short periods of time during pregnancy is considered to only have a small risk [17, 28].

Follow-up
Active disease should be assessed as clinically required. Stable disease should be reviewed after 1-3 months.

3. 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. In vulval clinics it may comprise 10-35% of patients seen. The condition usually develops in mid- to late-adult life [4].

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 atopy [4]

- 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 sclerosus or a fungal or yeast infection.

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 e.g. 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 [29]. The itch-scratch-itch cycle plays a pivotal role in maintaining chronicity of the condition.

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 damage [4]
- Vulval lichen simplex chronicus does *not* seem to be associated with a higher risk of squamous cell cancer [30]

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 (IV, C). 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 [2] (III,B)
- Serum ferritin [2] (IV, C). In case of suspicion of low iron store, e.g. in women who are vegetarian or donate blood.

Management

Recommended regimens

- Improvement of skin barrier function (saline soaks, followed and later replaced by lubricants- any unperfumed cream will do, petroleum-based lubricants too greasy) [4] (IV,C)
- Identifying underlying disease, if any
- In severe disease, superpotent topical corticosteroid, e.g. clobetasol propionate 0.05% ointment, once or twice daily (IV,C)
- In case of nighttime scratching: mildly sedative antihistamine (e.g. hydroxyzine), or tricyclic (e.g. amitriptyline) [4,31].

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 treatment [31,32]
- Narrow band ultraviolet B, delivered by comb-like instrument [33] (III,B)
- Silk fabric underwear may reduce the need for topical corticosteroids [34] (Ib,A).

Follow-up

- Mild disease: as clinically required

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

4. LICHEN SCLEROSUS

Lichen sclerosus (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. The signs in young girls may be difficult to distinguish from those of sexual abuse. LS is probably underdiagnosed. In females the course is usually chronic, but should be diagnosed as soon as possible, as early treatment prevents scarring and possibly malignant change. 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. 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 [35,36]. 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.

Symptoms

- Itch
- Soreness
- Dyspareunia or apareunia
- Urinary symptoms (pain, poor urinary stream)
- Other symptoms, e.g. constipation, can occur if there is perianal involvement, in particular in children
- Can be asymptomatic

Signs

- Pale, white hypertrophic or atrophic areas (vulva, perianal, extragenital)
- Hyperkeratosis
- Sclerosis
- Slight erythema / redness
- Purpura (ecchymosis) is common
- Fissuring anogenitally
- Erosions, but blistering is very rare
- Changes may be localised 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 (extragenital)

Complications

- Loss of self esteem (concern about the clitoral appearance)
- Development of squamous cell carcinoma (actual risk <5%)[37]
- 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. Clinical and pathological correlation is essential. In early disease histology can be non-specific.

Key histopathological features (biopsy has to be taken from a typical lesion) [38]:

- 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 (IV,C) [36]. 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, although this may be less in well controlled LS [39]. They should be advised to contact the doctor if they notice a change in appearance (e.g. lump, ulceration or hardening of skin), or if there is a major change in symptoms.

LS needs to be treated. About 10% of patients have no itch, but will have clinical signs of LS and should also be treated (IV, C). After initial treatment (usually 3 months) some patients will become asymptomatic with few remaining signs of LS, others may be left with irreversible scarring. There is debate amongst specialists about further treatment once symptoms and signs are suppressed by the initial treatment. This is because it can be difficult to decide whether there is still active disease. However, as it is known that LS may progress and lead to more scarring despite the lack of symptoms after initial treatment, some propose continuous, preventive treatment for many years in order to prevent progression (IV, C). Lee et al. in a recent series, with a mean follow up of 5 years, showed that continuous treatment with individually chosen applications of a topical steroid will prevent symptoms, further scarring and carcinoma development in 58% vs. 93.3%, 40% vs. 3.4% and 0% vs. 4.7%, respectively [39]. Emollients may give symptom relief after initial steroid treatment (IIb B) [40].

Specific treatment

Potent [41] or ultra-potent topical steroids [42] e.g. mometasone furoate or clobetasol proprionate are first line recommendations for genital LS (Ib, 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, 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 mometasone furoate 0.1% ointment is effective and safe in maintaining remission, and may help to prevent malignant change (Ib, A) [39, 43]. 30g of an ultra-potent steroid should last at least 3 months.

Treatment of superinfection

An ultra-potent or potent topical steroid preparation combined with antibacterial and antifungal agents e.g. 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 (IV, C).

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% has been demonstrated in the treatment of vulval LS [44] (Ib, A) and when used for 16 to 24 weeks in males and females with genital and extra genital LS [45] (IIb, B). Topical tacrolimus 0.03% ointment appears to be an effective treatment for children with anogenital LS and as maintenance treatment (twice a week), possibly reducing recurrences [46] (III, B). 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 [47] (Ib, A). Another study of pimecrolimus showed that 42% of patients were in 'complete remission' after 6 months application [45] (IIb, B). Local irritation was the most common side effect with both tacrolimus and pimecrolimus but usually improved after the initial period of use [48, 49]. The long-term risks need to be studied in view of concerns about the possibility of topical immunosuppression increasing risk of malignancy [50].

Limited data from two small RCTs demonstrates efficacy of systemic retinoids in the treatment of genital LS [51-53]. 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 2 years after finishing treatment (Ib, A). Topical hormonal therapy (progesterone or testosterone preparations) failed to demonstrate efficacy in controlled trials (IIa, B) [42].

Phototherapy is effective in some LS patients. In vulval LS, UVA1 may be considered if topical corticosteroids have failed. However, the well documented development of carcinomas after PUVA and UVB gives cause of concern, in particular at the genital site [54,55] (Ib, A).

Surgery in vulval LS should only be used for the treatment of coexistent VIN / SCC or fusion [56]. Disease tends to recur around the scar in females (III, B).

Clitoral LS

Lichen sclerosus may appear isolated at the clitoral hood, however, often other vulval parts are also affected. Early signs of clitoral LS are swelling of the prepuce; white plaques, fissures and scarring may follow. If the clitoral prepuce is affected by LS this may lead to fusion of the skin and a burrowed clitoris. Clitoral involvement should be searched for and treated like LS at other genital sites. As mechanical triggers are thought to be important in maintaining LS e.g. any tight clothing 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 counseling 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 [55,57] (Ib, A).
Potent topical steroids and topical calcipotriol, possibly under occlusion, may be tried in extragenital LS [57] (III, B).

Pregnancy and Breast-feeding

- 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 contraindicated during pregnancy and pregnancy must be avoided for at least 2 years after the end of treatment. Retinoids should be used with caution in all 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.

5. LICHEN PLANUS

Aetiology

Lichen planus 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. It is an inflammatory condition of unknown pathogenesis, but is probably 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 lichen planus of the vulva but are of unknown significance [58]. In some cases there is overlap between lichen planus and lichen sclerosus [59].

Symptoms

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

Signs

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

1. Classical
Typical papules occur on the keratinised 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 lichen planus may be asymptomatic. Vulval lesions were found in 19 out of 37 women with cutaneous lichen planus, with four of the 19 having had no symptoms [60].

2. 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.

3. Erosive
This the most common subtype to cause vulval symptoms. The mean age of onset of vulval symptoms in 114 women with erosive lichen planus was 56.9 years [61]. 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 recognise vaginal involvement in erosive lichen planus (which can occur in isolation) and start treatment early, as it can lead to scarring and complete stenosis. The lesions consist of friable telangiectases 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, synaechiae and scarring can develop [62]. This type is also seen in the oral mucosa although 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.

Diagnostic criteria for vulval erosive lichen planus have been proposed in an international e-Delphi exercise [63]. It is 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.

Complications
- Scarring, including vaginal synechiae.
- Development of squamous cell carcinoma. In one study the incidence was as high as 3% [61]. Patients with lichen planus-associated squamous cell carcinoma have a high rate of inguinal metastases, recurrent vulval cancers in diseased mucosa and disease-related death [64].

Diagnosis
Characteristic clinical appearance: involvement of the vagina excludes lichen sclerosus. Skin changes elsewhere can be helpful, but overlap between lichen planus and lichen sclerosus is described. Immunobullous disorders such as cicatricial mucous membrane pemphigoid and pemphigus can clinically resemble erosive lichen planus.
Dermoscopy: specific dermoscopic features that may aid clinical diagnosis include the presence of thick linear irregular vessels arranged diffusely throughout lesions, peripheral Wickham's striae and an intense red background [65].
Histology of vulval biopsy: irregular saw-toothed acanthosis, increased granular layer, basal cell liquefaction and band-like dermal mainly lymphocytic infiltrate [66].

Further investigations
- Biopsy is indicated if the diagnosis is uncertain or coexistent intraepithelial neoplasia/squamous cell carcinoma 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 lichen planus. Investigation for autoimmune disease is indicated if there is clinical suspicion of abnormality (IV,C) [67].
- 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 lichen planus found no evidence of increased incidence and concluded that routine screening is unnecessary [68]. Nevertheless screening may still be prudent in populations with a high prevalence of viral hepatitis.

Management
General Advice
Patients should be informed about the condition and given written information. Patients 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 is only one randomised controlled trial evidence to guide treatment of vulval erosive lichen planus [69, 70].

Topical Treatment
Recommended Regimen

- Ultrapotent topical steroids e.g. clobetasol proprionate. (IIb,B) In a study of 114 patients in a vulval clinic, 89 used ultra potent 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 [61]. 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. A proprietary preparation containing hydrocortisone (Colifoam® rectal foam) introduced into the vagina with an applicator, is useful. Prednisolone suppositories may be used in more severe cases (IV,C).

Alternative Regimens

- An ultra-potent topical steroid with antibacterial and antifungal e.g. clobetasol with neomycin and nystatin or an alternative preparation e.g. betametasone with fusidic acid or generic equivalent may be appropriate if secondary infection is a concern. These should only be used for a short period of time to clear infection (IV,C).
- The topical calcineurin inhibitors pimecrolimus and tacrolimus may be effective in vulval lichen planus; pimecrolimus may be better tolerated [71]. In a retrospective series of 16 women with vulval lichen planus, 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 [72].

Systemic treatments
There is no consensus and little evidence base for the use of systemic agents. In the vulvovaginal–gingival syndrome there is general agreement that azathioprine, dapsone, griseofulvin, chloroquine and minocycline, all tried empirically, are of little or no benefit. Cyclosporin may be considered.

- The retinoid acitretin can be helpful in hypertrophic cases. 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.
- Oral steroids are used, for example prednisolone 40 mg/day, tapered off over a few weeks, for severe flares; courses can be repeated as necessary.
- Long-term methotrexate 5-10mg weekly was used successfully in 11 of 131 patients with vulvovaginal lichen planus [73]
- Mycophenolate mofetil may be effective and worth considering for recalcitrant cases [74,75]

The new biological agents have shown varying results. However the rising trend of TNF-α inhibitors inducing lichen planus-like eruptions including erosive oral and vulval disease [76] reserves these drugs for only the most recalcitrant cases. Basiliximab was reported to be effective in erosive oral lichen planus, although its use has not been evaluated in vulval disease [77].

All these potentially toxic therapies need careful monitoring and are best supervised by a dermatologist in the context of a specialised clinic (IV, C).

Surgery
Surgery may be necessary for management of symptomatic vulval and vaginal adhesions and scarring, but is contraindicated in patients with active, inflammatory disease [78]. In a study of 11 women with lichen planus scarring, 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 [79].

<u>Pregnancy and Breast-feeding</u>

- Topical steroids are safe to use while pregnant or breast-feeding.
- Topical calcineurin inhibitors are contra-indicated whilst pregnant or breast-feeding [42].
- Retinoids are absolutely contraindicated during pregnancy. Pregnancy must be avoided for 2 years after finishing treatment and retinoids should be used with caution in all females of child-bearing age.

<u>Onward referral</u>
Referral to a multidisciplinary vulval clinic is recommended for erosive disease, recalcitrant cases or those in whom systemic therapy is considered.

<u>Follow-up</u>

- At 2-3 months to assess response to treatment.

- Active disease should be assessed as clinically required. Erosive vulval lichen planus needs long-term specialised follow-up (IV, C).
- 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).

6. VULVODYNIA

According to the 2003 International Society for the Study of Vulvovaginal Diseases (ISSVD) terminology, vulvodynia is defined as 'vulval discomfort, most often described as burning pain, occurring in the absence of relevant visible findings or a specific, clinically identifiable, neurologic disorder' [80]. Vulvodynia is also categorised by the ISSVD, as generalized or localized, provoked, unprovoked or mixed (both provoked and unprovoked) (see symptoms).

Aetiology

Vulvodynia is currently considered as a dysfunctional sensory processing in the central nervous system, involving both central and peripheral pain generators [81-83]. This mechanism is similarly observed in other painful conditions (fibromyalgia, interstitial cystitis/painful bladder, irritable bowel, temporomandibular dysfunction) which have a significant association with vulvodynia [84, 85]. A genetic predisposition to both vulvodynia and these other pain conditions is suspected [86]. Triggering or maintaining factors have been identified: candidiasis [87], psychological disturbances either resulting from the chronic pain or preexisting to it [88-90], and pelvic floor muscle dysfunction [91].

Symptoms

The mnemonic (memory aide) OPQRST-A can be used to describe and evaluate the vulval discomfort.

Onset

Candidiasis is frequently an initiating event of vulvodynia (IIb) but any acute painful vulval, urinary or anal condition (e.g. infection, surgical procedure) may precede the occurrence of vulvodynia, especially if these physical events occur in a context of emotional stress (IV).

Provocation

The discomfort may be either provoked or unprovoked or mixed.

1. Provoked
    a. 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).
    b. By non sexual contact : tampon insertion, tight clothing, sitting position, gynaecological exam
2. Unprovoked: the discomfort occurs spontaneously, it is not related to touch.
3. Mixed: the discomfort is both spontaneous and aggravated by local contacts (either sexual or non sexual).

Quality

Burning is the main symptom, but many other sensations are reported (e.g. tingling, stinging, rawness, irritation). When present, itch is not the predominant symptom.

Region

The discomfort may be either localised or generalised.

1. Generalised: 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.
2. Localised: one or several sites are involved. The most frequently involved site is the vestibule (i.e. the introitus), particularly its posterior aspect. This is termed vestibulodynia. Provoked vestibulodynia is the most reproducible subset of vulvodynia. More rarely, the discomfort is localised to other parts of the vulva: labia minora or majora, clitoris (clitorodynia).

Severity

The severity of the discomfort is highly variable, impacting both daily life (impossible to concentrate on normal activities) and sexual activity (painful sex leading to fear and avoidance, with consequences on the partner and relationship).

Time

Vulvodynia is a chronic pain condition having usually lasted months or years before the diagnosis is made. The intensity of the discomfort is often variable over time. Significant improvement or complete remission may occur, following treatment, or spontaneously (IIa) [92,93].

Associated symptoms
Other pain conditions (mentioned before) may be associated, particularly interstitial cystitis/painful bladder [94] (level B). No sphincter disturbance occurs in vulvodynia.

Signs
Inspection of the vulva reveals no relevant physical findings. This means that the vulva has a normal appearance or that, if a lesion is found, this lesion cannot explain the discomfort (e.g. a wart cannot explain diffuse burning). In provoked vestibulodynia, tenderness is elicited by gentle application of a cotton wool tip on the vestibule. Neurological examination is normal (in particular, there is no perineal anaesthesia).

Complications
Impact on general well-being, particularly on psychosexual function and relationships [95].

Diagnosis
It is a clinical diagnosis based on signs and symptoms.

Differential diagnosis
- Vulval conditions either inflammatory, infectious or neoplastic responsible for vulval discomfort are detectable by inspection.
- Neurological conditions responsible for perineal pain are suspected on sphincter disturbances and objective neurological abnomalities. Imaging (pelvic and lumbosacral MRI) is indicated in cases of spontaneous generalized vulval pain resistant to treatments (IV).

Management
Information
Patients should be given a full explanation of their condition verbally, and then reinforced with written information. 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 simply the current knowledge about mechanisms, contributing factors, treatment and prognosis.

Treatment
A multidisciplinary approach to patients with vulvodynia is widely recommended [96,97]. The levels of evidence are poor, however [98]. Delays in diagnosis and inappropriate treatments may have a negative prognostic impact.

Vulval care measures
- Avoidance of irritating factors (IV, C)
- Use of emollient soap substitute (IV, C).

Analgesic treatments
Local Pain Modifiers
Local anaesthetics, e.g. 5% lidocaine ointment or 2% lidocaine gel, are mainly prescribed in patients with introital dyspareunia resulting from provoked vestibulodynia. Lidocaine should be applied 15-20 minutes prior to penetrative sex and washed off just before penetration (IV, C). Long term daily use of lidocaine is commonly recommended in practice, although in one randomized controlled study, 12 week application of 5% lidocaïne 4 times a day was not more effective than placebo in reducing vestibular pain [99] (I, A).

Others
- Botulinum toxin: not superior to placebo [100] (Ib, A)
- 2 to 6 % gabapentin cream [101] (III, C)
- 2 % amitriptyline cream [102] (III, C)
- 0.025 % to 0.05 % capsaicin cream [103,104] (III, C): use limited by topical side effect (burning).

Oral pain modifiers
Mostly prescribed in case of unprovoked vulvodynia. Amitriptyline is a tricyclic antidepressant with analgesic properties. Low doses of amitriptyline (titration from 5 to 25 mg daily) are widely used, although one randomized study has not confirmed the beneficial effect of this treatment in vulvodynia [105] (Ib, A).

Gabapentin, an anticonvulsant, is another treatment of neuropathic pain at an initial dose of 300 mg per day, with an increase up to 1200 mg [106] (III, B). There is little evidence for the use of pregabalin [107] (IIb, B).

Multilevel anaesthetic nerve blocks (caudal, pudendal) [108,109] (III,C)

Neuromodulation

Transcutaneous Electrical Nerve stimulation (TENS) may be a self administered home protocol. [110,111] (Ib, B).

Acupuncture [112] (Ib, B)

Physical therapies
Pelvic floor muscle dysfunction should be addressed in patients with vulvodynia, particularly when introital dyspareunia is present.

- Perineal manual therapy and biofeedback [113] (III, B): best results with physiotherapists experienced in the management of chronic vulval pain and its sexual impact (IV, C).
- Vaginal trainers [114] (III, B).

Psychosexual interventions
Cognitive-behavioural therapy (CBT) [115,116] (III, C) is the mainstay approach and is superior to supportive psychotherapy [117] (Ib, A)**.** As dyspareunia affects the sexual well-being of both the patient and her partner [118], couples' CBT therapy seems a logical approach [119] (III, C). Mindfulness has also been used [120] (IV, C).

Surgery
Vestibulectomy (posterior or total; with or without vaginal advancement to cover the defect) is usually considered a "last resort", after failure of all the available therapeutical options [121]. However the level of evidence is low [122] (III, C) and one study shows that, at long term follow-up, vestibulectomy is not more effective that CBT [123,124]. In addition, surgery may aggravate pain related to a dysfunction in pain processing.

Follow-up

- Every 3 months until improvement (IV)
- Multidisciplinary long-term follow-up (IV).

7. VULVAL INTRAEPITHELIAL NEOPLASIA (VIN)

Introduction
VIN is a chronic vulval skin disorder characterized by dysplastic changes of the squamous epithelium. VIN is a premalignant lesion, although spontaneous regression has been reported [125]. 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 of VIN in 1922: " dyskeratose erythroplasiforme de la muqueuse vulvaire" [126]. The International Society for the Study of Vulvovaginal Disease (ISSVD) had been leading in the process of chosing 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 type [127]

Table 1. Evolution of the ISSVD terminology

Friedrich (1976) [128]	Wilkinson et al (1986) [129]	Sideri et al (2004) [130]	Bornstein et al (2016) [127]
Vulval atypia	VIN 1	Flat condyloma or HPV effect	LSIL
A. without dystrophy	Vin 2	VIN, usual type	HSIL
B. with dystrophy			
Squamous carcinoma in situ	VIN 3	VIN usual type	HSIL
	Differentiated VIN	VIN differentiated type	DVIN, differentiated-type VIN

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 [131], with the highest peak between 35-49 years [132]. 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 immuno-compromised state.
DVIN is associated with lichen sclerosus and lichen planus 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 [133,134]. 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).

Investigation

HSIL

Biopsy

- Histopathological characteristics: disorganisation of squamaous 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

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 [135].

- Surgical cold knife excision
- Laser CO_2 therapy
- Loop electrosurgical procedure (LEEP)
- Imiquimod cream
- Follow up without treatment (spontaneous regression)

DVIN

- Surgical cold knife excision

Follow up

Close follow-up is mandatory, life long

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. The quadrivalent HPV 6/11/16/18 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 [136].

Websites with useful patient information

British Association of Dermatologists

http://www.bad.org.uk/shared/get-file.ashx?id=180&itemtype=document

http://www.bad.org.uk/shared/get-file.ashx?id=113&itemtype=document

International Society for the Study of Vulvo-vaginal Disease

http://issvd.org/wordpress/wp-content/uploads/2014/09/ContactDermatitis-2013-final.pdf

British Contact Dermatitis Society Patient Information on specific allergens

http://www.cutaneousallergy.org/downloads/patient/standard/

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List of contributing organisations (see: www.iusti.org/regions/Europe/euroguidelines.htm)

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Appendices:

Search strategy:

Searched libraries: MEDLINE, MEDLINE process, Embase, Cochrane library. Sexually transmitted diseases guidelines produced by the British Association for Sexual Health and HIV (www.bashh.org) were also reviewed.

Search up to March 2015 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, Vulval pain syndromes/vulvodynia.

Tables of levels of evidence and grading of recommendations:

(see: http://www.iusti.org/regions/Europe/pdf/2013/Levels_of_Evidence.pdf)