Universitat de Girona

HTVC Hospital de Tortosa Verge de la Cinta

Clinical and demographic profile of women diagnosed with vulvar lichen sclerosus in the region of Terres de l'Ebre

A multi-centric observational study

Facultat de Medicina, Universitat de Girona

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“Great things are done by a series of small things brought together”
– Vincent Van Gogh

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1 ABBREVIATIONS

ABS	Àrea Bàsica de Salut
ACOG	American College of Obstetricians and Gynaecologists
AEEM	Asociación Española para el Estudio de la Menopausia
AEPCC	Asociación Española de Patología Cervical y Colposcopia
CEIC	Comitè Ètic d'Investigació Clínica
dVIN	Differentiated vulvar intraepithelial neoplasia
ECAP	Estació Clínica d'Atenció Primària
ECM 1	Extracellular matrix protein 1
EGB	Educación General Básica
FDA	Food and Drug Administration
FSFI	Female Sexual Function Index
GC	General coordinator
GP	General practitioner
HRQoL	Health-Related Quality of Life
HTVC	Hospital de Tortosa Verge de la Cinta
HPV	Human papilloma virus
ICS	Institut Català de la Salut
INE	Instituto Nacional de Estadística
ISSVD	International Society for the Study of Vulvovaginal Diseases
LP	Lichen planus
LS	Lichen sclerosus
LSC	Lichen simplex chronicus
MHPTC	Medium-high potency corticoid
QoL	Quality of Life
RA	Rheumatoid arthritis
SA	Statistics analyst
SAP	Sistema de gestió administrativa de pacients
SCC	Squamous cell carcinoma
SEGO	Sociedad Española de Ginecología y Obstetricia
SLE	Systemic lupus erythematosus
TCS	Topical corticosteroids treatment
UBE	Unidades de bebida estándar
UPTCS	Ultrapotent topical corticosteroids

uVIN	Usual VIN
VIN	Vulvar intraepithelial neoplasia
VLS	Vulvar lichen sclerosus
VSCC	Vulvar squamous cell carcinoma
KP	Koebner phenomenon

2 ABSTRACT

Background: vulvar lichen sclerosus (VLS) is a chronic inflammatory, non-neoplastic and non-infectious vulvar dermatosis with a relapsing and evolutive course. It occurs in all ages, but especially in post-menopausal women. Estimated prevalence is around 3%; otherwise, VLS incidence is reportedly rising. The aetiology of LS is still unknown, but data suggests a multifactorial origin including a genetic, autoimmune, hormonal, and local and systemic infectious backdrop. Symptoms include intense pruritus, pain, burning and dyspareunia. The typical lesions are white plaques and papules, often with areas of ecchymosis, excoriation and ulceration. VLS affects inter-labial sulci, labia minora, clitoral hood, clitoris, perineum and the perianal region. This cutaneous disorder can lead to destruction of the vulvar architecture, with scarring of the clitoral prepuce, resorption of the labia minora and narrowing of the introitus. Therefore, it can end up with a negative repercussion on the sexual function and quality of life of these women. In the vast majority of patients, it is a benign disease, but malignancy transformation can occur. It should be diagnosed as soon as possible, as early treatment is needed in order to prevent scarring and possible malignant change and it is essential for patients to be counselled that long-term treatment and follow-up is very important. Additional research is needed to identify the optimal potency, dosing, and duration of use.

Objective: our main objective will be to determine the clinical and demographic profile of women diagnosed with vulvar lichen sclerosus (VLS) in the region of Terres de l'Ebre.

Design: this is a multi-centric observational, descriptive, population and transversal study. It will be conducted in the different medical centres with gynaecological assistance in the region of Terres de l'Ebre belonging to *Institut Català de la Salut* (ICS), where the hospital of reference is Hospital de Tortosa Verge de la Cinta (HTVC) between March 2021 to March 2025.

Participants: the study will include patients over 18 years old, clinically and pathologically diagnosed with vulvar lichen sclerosus.

Methods: data will be obtained from patient's medical records, a patients' questionnaire and three different scores. A consecutive non-probabilistic sampling will be used to recruit the 282 patients required.

Keywords: lichen sclerosus, vulvar lichen sclerosus, introitus, vulvar cancer, squamous cell carcinoma, vulvar intraepithelial neoplasia.

3 INTRODUCTION

3.1 DEFINITION OF VULVAR DERMATOSIS

The vulva, like the rest of the skin, can be affected by numerous dermatological conditions like inflammatory dermatoses, infections, tumours, pigmentation alterations, chronic pain, etc. There is a lot of work behind to classificate these conditions in order to diagnose and treat the patients who suffer from them. Vulvar inflammatory dermatoses of the vulva constitute a very frequent reason of consultation in the clinical assistance (1). They are a very heterogeneous group of lesions, due to a great variety of their clinical presentation and evolution too (1) and its particular anatomic and physiologic characteristics create an emerging new branch of dermatology (2) otherwise they have also been assessed mainly by gynaecologists (1). They are inflammatory conditions responsible for chronic or recurrent itching and soreness, and lichen sclerosus (LS) is one of them (3). The lesions are either circumscribed to the vulva or associated with extra genital localizations which may help to assess the diagnosis (3). Therefore, these conditions are necessarily a multi-specialist disease including, as well as others, gynaecologists, dermatologist and pathologists.

The International Society for the Study of Vulvovaginal Diseases (ISSVD) made a histological classification in 2006 (Figure 1) (1) (Annex 1).

3.2 ISSVD TERMINOLOGY AND CLASSIFICCATION OF VULVAR DERMATOLOGICAL DISORDERS

The International Society for the Study of Vulvovaginal Diseases (ISSVD) over the years, has had a goal, which is to develop and promulgate a nomenclature (or terminology) and classification of vulvar diseases, especially of the vulvar dermatosis. These are multidisciplinary illnesses, so this society felt the need to create a universal language about vulvar dermatosis in order to facilitate the diagnosis by the clinicians and promote the best care for the patient. The ISSVD was found and it's formed by a multinational group of gynaecologists, dermatologist and pathologists (1).

About recognizing diseases, a clinician can do it by the examination (and additional knowledge) or, if this is not possible, a biopsy can be run and the pathologist can identify the specific diagnosis. But, when neither the clinical nor the pathologist can determine a single diagnosis, we need a correlation between a histologic pattern and the diseases most commonly demonstrating this pattern, plus the most clinical information about the patient and its examination. This last situation was the "problem" which the ISSVD committee observed and so the motivation to construct a classification system of vulvar dermatosis, because, many times, they're difficult to diagnose accurately and distinguish (2).

First, in 2006, they carried out a classification based on the histological patterns, divided into 8 groups (Annex 1) (1). Neoplasms (both benign and malignant) and infectious diseases are not included. The reason why neoplasms are not included is because the members who carried out the classification thought that they have a sufficiently histologically distinctive pattern to be recognized. In the same way infectious diseases are not included because they have a well-defined clinical criteria for diagnosis. Despite this, benign inflammatory diseases are the most diagnostically troublesome because the conditions are clinically difficult to recognize. This is because their characteristic morphologic hallmarks can be concealed because of the vulva environment (such as warm, moist and frictional). With these ideas, they elected for the classification the non-infectious and non-neoplastic vulvar diseases, included as "vulvar dermatoses". Their aim was, also, to make it simple and useful, so they included only the most common and most important histologic patterns and diseases, following the well-stablished dermatologic terminology (1).

A few years later, in 2011, the ISSVD formulated a new approach to, again, diagnose vulvar dermatoses, but in this case, the aim then was to make highly accurate diagnoses with the clinical setting (Table 1) (2) (Annex 2). There are literally hundreds of disorders that involve the vulva, but this classification includes 106 vulvar disorders, considering clinical history and examination (3).

In dermatological diseases, a simple visual examination provides almost all of the information needed to arrive at a correct diagnosis. So, diseases with similar visual characteristics are grouped (classified) into clusters. With this idea, then, they created a relatively short list of differential diagnosis. It should be noted that, this classification only includes characteristics of visual lesions.

Another objective of this clinical approach was to complement the histological one from 2006, so they do not exclude each-other and the 2011 ISSVD classification does not supplant the 2006 ISSVD classification. Therefore, the focus of this new 2011 classification involves an examination and describes 5 steps we should follow in order to achieve the most accurate diagnosis as possible (Annex 3) (2).

If more than 1 lesion is present, the most prototypical lesion should be chosen for the purposes of description.

So, in this ISSVD 2011 classification, diseases are listed in the 8 morphological groups that include about 50 of the most commonly encountered disorders (Table 1) (2) (Annex 2). It does not include those disorders presenting solely with symptoms.

They also included a clarification about lichenified nomenclature, because they opine that it's particularly confusing.

- *Lichenification*: develops as a result of chronic scratching and/or rubbing (the "itch-scratch cycle"). It is characterized clinically by a palpable thickening of the tissue and increased prominence of skin markings. It is also characterized by an "acanthotic pattern". It may be superimposed on some other underlying dermatological disorder.

3.3 DEFINITION OF LICHEN SCLEROSUS (LS)

LS is the most common vulvar inflammatory dermatosis with the potential exception of contact dermatitis. LS was first described by Hallopeau in 1887 and over time has also been termed differently (4). In the ISSVD last classification, it appears as *Lichen Sclerosus* (2).

Is a chronic, inflammatory, non-neoplastic and non-infectious in nature cutaneous disorder that can leads to scarring, impaired sexual function, and malignancy. While LS can affect any area of the body of both males and females, it has a predilection for female ano-genital epithelium (85–98% of cases), predominantly affecting the genital skin and mucosa, with extra-genital lesions in 15–20% of patients (5). In our project we will only study the effects it has in females. The disease affects inter-labial sulci, labia minora, clitoral hood, clitoris, perineum and the perianal region (6) with whitening lesions with a converge tendency and can lead to architectural loss of the vulva. The vagina and cervix (6) are not affected and very rarely involves the oral mucosa (7). It should be diagnosed as soon as possible, as early treatment is needed in order to prevent scarring and possibly malignant change (7). It typically has a chronic but relapsing course. There is no specific treatment and neither is there a cure (3) (4) (8), although spontaneous remission can be observed (7).

The coexistence of LS with lesions from lichen planus (LP) and morphea or localized scleroderma has been described many times at the same time and, even, with systemic scleroderma (9). It has a repercussion in cutaneous, urinary and sexual health (10).

3.4 EPIDEMIOLOGY

Lichen sclerosus is relatively rare; exact prevalence is unknown (11). Vulvovaginal LS estimated prevalence is 1:30 (around 3%) (12). Otherwise, the incidence of VLS is reportedly rising (9).

It still seems unknown and underestimated because some patients are asymptomatic (a third of cases are asymptomatic (9)), and it is frequently misdiagnosed (13). Another reason could the variety of specialists who treat LS (13).

Both sexes are affected, but it is more common in women than in men; the exact ratio is unknown. According to different studies female to male ratio varies from 1:1 to 10:1 (14) and Bethanee J. Schlosser et al. states 6 to 10 times more frequently in females than in males (4).

The majority of revised bibliography asserts that there is no racial preference or predilection. However, other studies manifest that LS is more frequently diagnosed in Caucasian or White race; this could be due to a better health care access but it could also suggest an association with autoimmune diseases or genetic factors (12) (13).

It occurs at all ages (14), but it most commonly affects peri-menopausal and post-menopausal women (15), especially post-menopausal (16) (17). The presentation is bimodal, one in pre-pubertal girls (average age: 7.6 years) and the other in peri- and post-menopausal women (average age: 52.6 years). However, many cases also present during reproductive years (9). This distribution suggest a relation with hormonal factors, even though, this relation has not been proved (12). Of notable importance, however, is that a substantial number of women (17% to 40%) will experience the onset of symptoms and cutaneous changes of VLS during the reproductive years (4).

3.5 PHYSIOPATHOLOGY

The aetiology of LS is still unknown, but several mechanisms have been studied for this and epidemiologic data suggest a multifactorial origin, including a genetic, autoimmune, hormonal, and local and systemic infectious background.

3.5.1 Genetic Factor or Genetic Predisposing

Evidence suggests that LS is an autoimmune disorder with a genetic component (8). Genetic associations are seen in patients of both sexes (6). This has been reported in a study where 12% of female patients with vulvar LS reported a first-degree female relative with the same condition (8). So, family history of the condition is suggested in many articles (18). Different forms of familiar aggregation have been described. Some classic studies describe LS in twins (both monozygotic or heterozygotes), father-daughter, mother-son, etc. (8).

In genetically predisposed people, an extern success like trauma, wound or sexual abuse can be the trigger and lead to the development of LS. This suggests the Koebner phenomenon (12). There is also an association with epigenetic altercations (6).

Some studies indicate a significant association of LS with genes regulating human leukocyte antigen (HLA) class II antigens, which are involved in humoral immunity. They show that these female patients have an increased prevalence of HLA-DQ7, HLA–DQ8, HLA–DQ9, and HLA –DR12, being HLA-DQ7 the most frequent and it seems to be related to the early beginning of the disease. Whereas HLA-DR17 seems to be a protective factor (5) (8).

3.5.2 Autoimmunity

There are different arguments supporting this mechanism.

3.5.2.1 Infiltration by lymphoid cells.

Development and persistence of LS is linked with dermis infiltration by lymphoid cells. In a recent study it is shown that mononuclear T cells infiltration with cytotoxic activity is high, and many of them were near the hydropic degeneration area in the basal layer. In fact, it has been described that upregulation of T_h1 cells plays a role in inducing autoimmunity (8). Because of that, it is possible that these cells have an important role within the disease pathology (10).

3.5.2.2 Association with other autoimmune conditions

Many studies agree with this fact. More frequent diseases are autoimmune thyroid diseases (Hashimoto thyroiditis and Graves' disease), alopecia areata, vitiligo, pernicious anaemia (gastric parietal cells auto-antibodies), systemic lupus erythematous (SLE) (10), diabetes mellitus (DM) (19) and celiac disease (12). Autoimmune thyroiditis seems to be much more common, but the *Asociación Española de Patología Cervical i Colposcopia* (AEPCC) suggests that they have not detected a specific autoimmune disease is more prevalent than another autoimmune disease. So, the question comes up here if these patients should undergo screening for other immune diseases, in particular thyroid disease, although current guidelines recommend only clinical evaluation (8). Also, an increased incidence of autoantibodies to the extracellular matrix protein 1 (ECM 1) and autoantibodies to BP180 antigen are reported, but there's no clinical nor a pathological relevance (7) (12) and recent studies indicate that autoimmunity to ECM1 alone is not sufficient in explaining the pathogenesis of LS (8). Both autoantibodies to ECM1 and dysregulation of a protein regulated by p53 promote an overactive collagen synthesis and disruption of the basement membrane, which leads to thickening and therefore to sclerotic tissue formation (8).

3.5.3 Hormonal Component

Due to the bimodal distribution of the disease (post-menopausal women and pre-pubertal girls) and the improvement in many child cases with hormonal development, association with low estrogenic levels in physiologic states is suggested. In the same way, altered hormonal axis is suggested as a possible contributory factor (5).

However, there are no studies proving a protective effect from estrogens and, even more, lack of improvement or efficiency with use of contraceptive pills points to a controversial role of hormones (5) (9) (10) (12).

3.5.4 Hypopigmentation

Hypopigmentation present in LS has been interpreted as an autoimmune reaction against melanocytes-cells, which is the same in vitiligo disease (12).

3.5.5 Infectious Aetiology

There is not enough evidence and it is contradictory, but it has been suggested that infectious agents could be implicated with LS development as a trigger.

The most revised is *Borrelia burgdorferi*, causative agent of Lyme disease. However, several studies don't show this association in the U.S.A., some doubt still remains in Europe and there is no evidence for a link in the U.K (6).

Others are viral aetiology associated with Human Papilloma virus (HPV) (16), Epstein-Barr virus (EBV) and Hepatitis C virus (HCV). *Streptococcus* infection has been mentioned too (10). A chronic vaginal infection can act as an antigen and set off immunologic mechanisms in the affected area.

Some authors have demonstrated the presence of HPV in LS lesions (19) and a recent study backs this theory based on LS improvement of women treated with combination of corticoids and imiquimod (20). Otherwise, some authors couldn't demonstrate this relation.

3.5.6 Local Causes

Koebner (or isomorphism) phenomenon is a well-known manifestation. It is described as the occurrence of lesions at sites of injury. In this case, we refer to traumatized skin due to scratching or sexual activity, repeated irritation or friction, surgical wounds and radiation (radiotherapy and sunburn) (6). This phenomenon is of particular relevance in LS which presents hyperplasia

secondary to the scratching due to an intense pruritus (12). This phenomenon is also termed the isomorphic response, because the new lesions that appear are clinically and histologically identical to the patient's underlying cutaneous disease (21).

3.6 EVOLUTION

As explained before, lichen sclerosus (LS) can appear at any age and in both male and female. It is a chronic condition with a relapsing and remitting course. Its natural history is not well known.

In this paper, we will explain a little bit of the evolution of the disease in the female.

In paediatric VLS the mean age of diagnosis is 6.7 years old (range 3 to 14 years old), that is later than the presentation (delay of 1-2 years) (22). Perianal involvement and dysuria resulting from fissuring are common at this period of time. It was believed to be resolved by puberty, but nowadays there are studies proving that the majority of these patients still have active disease after menarche or puberty and so, are at risk for progressive agglutination and scarring and, thus, persistence in adulthood (4) (23). Due to this data, it is important to undertake a long follow-up and accurate education on the disease. Malignancy has not been reported (6).

Meanwhile, in the case of women in reproductive years, a non-contemptible number of them (17% to 40%) will experience onset of symptoms and cutaneous changes of VLS during this period of time (4).

As in pregnancy, clinical experience demonstrates that LS improves with less treatment required. Vaginal delivery can be assessed. It's important to be careful with de Koebner effect, because obstetric scars can arise (6). We would like to remember that Koebner phenomenon (KP) is the appearance of new skin lesions on previously unaffected skin secondary to trauma (24).

Nevertheless, in the vast majority of patients it is a benign disease, but complications can occur (see "3.9 COMPLICATIONS" section). Exceptionally, it can turn into squamous cell carcinoma (SCC) (see "3.10 RISK OF MALIGNANCY" section) (25).

In a study of 83 women with VLS, the cumulative incidence of relapse after ending treatment was estimated at 50% at 16 months and 84% at 4 years (26).

3.7 DIAGNOSIS

The diagnosis is made basically with the exploration of the vulva to observe if characteristic clinical appearance of LS is present. In this part, we would recommend following the five steps proposed by the ISSVD in order to achieve a diagnosis or if more lesions are present (Annex 3).

Although a biopsy is not required to confirm the diagnoses in typical cases, many clinicians prefer to take a biopsy at presentation (7). Two main reasons are because other vulvar diseases can mimic lichen sclerosus (6), and patients with LS, especially the untreated ones, are at increased risk of VSCC. Thereby, some of the indications to perform a biopsy are when diagnosis by clinical exploration is uncertain, if there are atypical features, presence of any nodular, bleeding or erythematous lesion, ulcers, any persistent erosions and suspected LS refractory to treatment among others (6) (7) (12). Clinical and pathological correlation is essential.

LS presentation can be diversified, both for symptoms and signs (12). Rarely LS may be asymptomatic (6). It is estimated that a third of patients are asymptomatic (17) or paucisymptomatics (12).

3.7.1 Symptoms (7) (27)

Patients with LS mostly report vulvar pruritus, irritation, burning, dyspareunia, and tearing.

- **Vulvar pruritus or itch** is the cardinal symptom and is present in the vast majority of patients. Frequently it is present in the evening and it can be so intense as to cause sleeplessness for the patient. Often it is merged with burning, irritation, and tenesmus.
- **Soreness**
- **Dyspareunia or apareunia if introital narrowing:** quality of life (QoL) can be truly affected. In the first stages it can be due to inflammation and in the latest ones, consequences from introitus stenosis or fissures are the cause. Hence, dyspareunia occurs in the presence of erosions, fissures or introital narrowing (6). Some women can even experience anorgasmia or the impossibility of intercourse (28).
- **Urinary symptoms** (dysuria, poor urinary stream or even urinary incontinence (17)): is the result of the labia minora fusion over the meatus, with its consequent stenosis. They occur in advanced stages of the illness. 30% of patients can experience urinary incontinence but it is not as common in the general population (29).

- **Anal symptoms**. They will exist if perianal involvement is present, but this is more common in children. Symptoms can be proctalgia, pruritus, anal cracks, haemorrhagic defecations and chronic constipation (12).

3.7.2 Signs (7) (27)

- Pale or white atrophic areas (vulva, perianal or extra-genital)
- Pale or white hypertrophic areas (vulva, perianal, extra-genital)
- Hyperkeratosis can occur
- Sclerosis
- Scratch signs or excoriation (Fig 2. (30))
- Slight erythema/redness
- Purpura (ecchymosis) (Fig. 3 (25))
- Fissuring anogenitally
- Erosions (Fig. 2 (30))
- Tearing
- Blistering is unusual
- Changes may be distributed from the superior vulva to the perianal tissue and can show up in the classic "figure of eight" or "hourglass shape" (Fig.4 (31)) .
- Scarring may lead to loss of architecture (loss of the labia minora and/or fusing the midline with clitoral burying, but not its loss) (Fig. 5 (8)).
- Introital stenosis (Fig. 5 (8))
- Follicular plugging

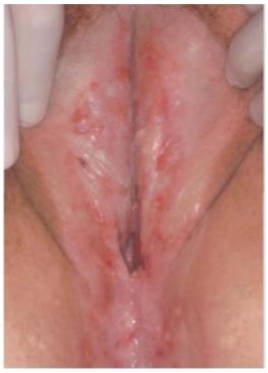

Figure 2. Erosions and excoriations (30)

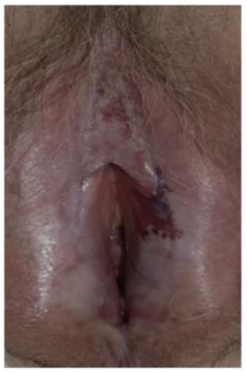

Figure 3. Ecchymosis (25)

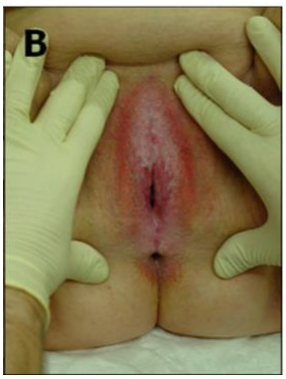

Figure 4. Typical "figure of eight" (31)

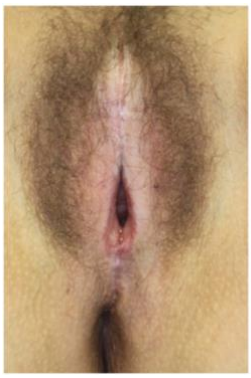

Figure 5. Labial resorption, phimosis of the clitoris and narrowing of the introitus (8)

3.7.3 Skin Features

Now, we would like to emphasize the guiding or key lesions that, when examined, should highlight the possibility of LS. A vulvoscopy will be necessary and also referral to a specialist if

we assist in primary care. We highlight the importance of an early diagnosis and treatment to prevent architectural changes and irreversible damage.

Figure 6. Perineal and peri-anal affection (10)

The characteristic involved sites are the inter-labial sulci, labia minora, clitoral hood, clitoris and perineal body (6) (Fig.6 (10)).

Typical LS lesions appear as porcelain-white or pallid-grey papules and plaques (Fig.7 (30)) often with areas of ecchymosis (or purpura), fibrosis and scarring (32). Follicular delling and hyperkeratosy can be prominent (6). We should pay attention if the classic "figure of eight" or "hourglass shape" is present (3) (32). The skin can also commonly appears thinned (atrophic in histology study), whitened, and crinkled ("cigarette paper" or "cellophane appearance") (Fig. 8 (33)).

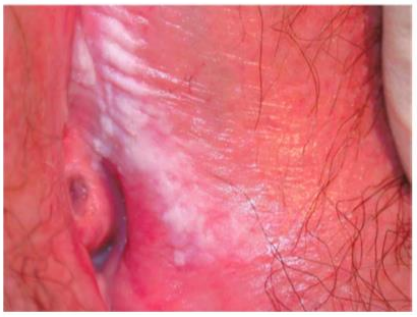

Figure 7. Porcelain white plaques (30)

Despite that the genital mucosa is largely spared, involvement of the mucocutaneous junctions can lead to introital narrowing. Other findings include fusion of the labia minora, phimosis of the clitoral hood and fissures (32).

As long as it is a chronic and evolving disease, findings can change depending on the stage of the condition. The *Asociación Española de patología cervical i colposcopia* (AEPCC) (12) classifies them in three periods:

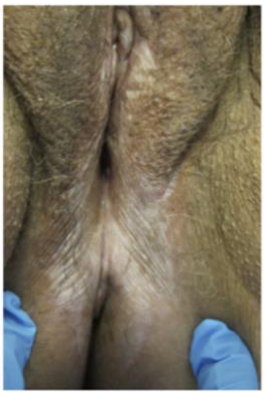

Figure 8. Cigarette paper-like appearance (33)

- **Early observations:**
  - Irregular, bright or porcelain-white or smooth papules or macular-papules, which tend to convert until the formation of plain plaques and low-lying (or sunken). In order of frequency, the affected areas are: labia majora and/or minora, perineum body, clitoris, and around the anus. Furthermore, they can expand until genitocrural folds and buttocks (6).
  - Characteristically, these cutaneous changes have a symmetric distribution.
  - Vanishing of Fordyce glands (12).
  - Vulvar anatomy and morphology still remain unimpaired.
- **Stablished disease:**

    - Remarkable atrophied skin, fragile, dull white colour with "smoking paper" appearance.
    - Abrasions and mild lichenification as a side effect from scratching, often times associated with labia majora oedema.
    - Telangiectasia and purpuras due to cutaneous atrophy (12).
- **Final stages**, where we find structural changes in the anatomy secondary to:
    - Sclerosis and scarring, but more evident than in previous stages.
    - Resorption of the labia minora, sealing of the clitoral hood and covering of the clitoris due to scarring.
    - In several and advanced cases, this fusion can lead to an occlusion more or less severe of the introitus (*craurosis vulvar*) (12).
    - LS does not affect, or rarely, the vaginal mucosa (however, case reports indicate vaginal disease may be more common than once thought and may be underdiagnosed (8)), and neither the cervix; in fact if it is altered, we should make the differential diagnosis with lichen planus (LP). If there is a vaginal prolapse, the mucosa may become keratinized and develop the disease (6).

3.8 DIFFERENTIAL DIAGNOSIS

Frequently, it is difficult to make an accurate diagnosis and it is easy to confound the following conditions, and this can lead to a misdiagnose or diagnostic delay of up to five years (34).

The differential diagnosis of LS should be done with conditions with similar signs and symptoms (12).

- **Vulvar Intraepithelial Neoplasia (VIN):** maybe the most important affliction we should reject. Remember that, in this situation, the associated type is the differentiated VIN (dVIN) and its presentation is such heterogeneous about colour, surface and localization. Half of them can be revealed with itchiness, pain and burning. About the histology, it appears as thickening of the epithelium with elongated and anastomosed interpapillary ridges and atypical mitosis figures (35).
- **Lichen planus (LP)**: intense pruritus and morphology alteration can be so similar to LS. However, LP usually affects the vagina, leading to inflammation and synechiae. We cannot forget that both dermatoses can occur together at the same time (12).
- **Lichen simplex chronicus (LSC)**: the main symptom is vulvar pruritus, but, in this case, it is caused by a chronic aggression; so, it is considered a cutaneous reaction (12).

- **Psoriasis**: again, it is a cause of pruritus, but lesions tend to be more erythematous than white (12).
- **Contact dermatitis:** it can affect all ages and is presented by acute or chronic itching or burning. The lesions are poorly demarcated, and we can find various degrees of erythema. A biopsy is only recommended if the diagnosis is uncertain.
- **Mucous membrane pemphigoid**: it is a bullous dermatosis characterized by erosive inflammatory episodes that heal giving rise to sclerosing lesions. We must suspect it when we observe great synechia in the labia (12).
- **Vitiligo**: it is a chronic skin condition that causes loss of pigmentation, resulting in irregular pale patches of skin. We can confuse it with barely symptomatic forms of LS (12).
- **Estrogenic deficiency**: we basically talk about Genito-urinary Syndrome of menopause. It may lead to cutaneous thickening and vulvar labia adhesion and, therefore, to dyspareunia. If the topic corticoid treatment improves the symptoms in two weeks, possibly we are aware of this condition. Non-response should assess a vulvar biopsy to exclude LS (5).
- **Common causes of vulvovaginitis**: candidiasis, bacterial vaginosis and trichomoniasis; particularly in their more complicated forms. In candida albicans infections the main symptoms will be pruritus and pain, but in non-albicans candida there will be burning rather than itching and less inflammation (32). Commonly, VLS is misdiagnosed as *Candida albicans infection* (9). As clinicians, we must be aware of the possibility of coexisting bacterial or fungal infections with VLS (5).
- **Genital HPV infection**: as we see in clinical practice, they exist normally in younger women than in LS; they can be immunosuppressed and vulvar epithelial disorders can be associated (36).
- **Paget disease**: an uncommon intraepithelial adenocarcinoma that affects mostly women of an average age of 65 years old. It appears as erythematous and white well-defined patches or plaques, irregular borders and eczematous appearance. Main symptoms are chronic itching and burning. In the histological study, the Paget cells are characteristic (17).
- **Systemic diseases**: such as Crohn disease (37) and hidradenitis suppurativa (38) can manifest as chronic vulvar pruritus.
- **Vulvodynia**: characterized by discomfort and pain in the absence of visible findings or an identifiable cause (39).

- **Localized scleroderma** (9)
- **Leucoplakia** (9)
- **Cutaneous patch of Lyme's** (9)

We would like to sum up the main differences between the common vulvar dermatoses with Table 2 adapted from Colleen K. Stockdale et al. (32) (Annex 4).

3.9 COMPLICATIONS

They appear mostly in advanced or mistreated LS.

- Histologic changes such as atrophy, hyperplasia or follicular plug (4)
- Loss of the vulva architecture (Fig.9 (40)). Scarring and deformity leads to:
  - Anal and urethra stenosis (9)
  - Fusion and loss of the labia majora and minora (12) (Fig. 10 (41)).
  - Introital stenosis: making sexual intercourse impossible and reduce health-related quality of life (HRQoL) (12) (Fig. 10 (41))
  - Development of clitoral pseudo cyst or clitoris burying (27)
- Sore areas (6)
- Secondary infections: candidiasis, herpes virus or HPV (42)
- Dysesthesia (42)
- Abrasions and skin cracks (12)
- Ecchymosis and bleeding (7)
- Urinary incontinence: present in 30% of patients, which worsens the symptomatology (27)

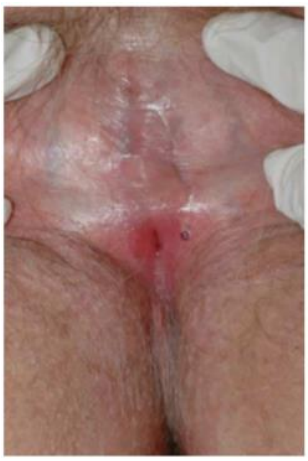

Figure 9. Resorption of vulvar architecture (40)

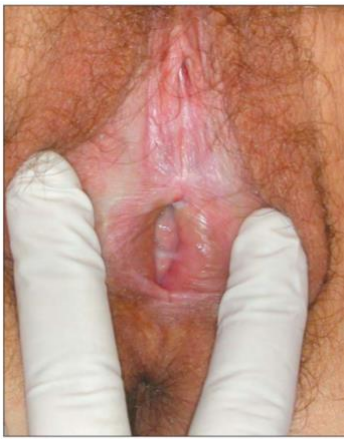

Figure 10. Resorption of the labia minora and narrowing of the introitus (41)

- Dysuria and difficulty in voiding: especially when there is a fusion of the labia minora over the urethra in advanced disease (5)
- Transformation to a premalignant or a malignant lesion (differentiated vulvar intraepithelial neoplasia - dVIN- or squamous cell carcinoma - SCC-) (27). (Fig. 11 (31)).

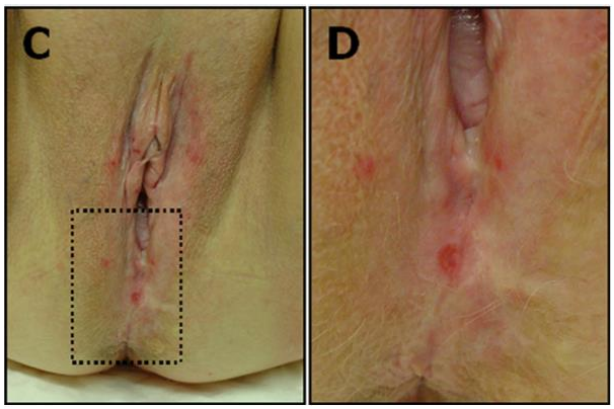

Figure 11. (C) Differentiated VIN. (D) A close-up of the differentiated VIN lesion (31)

- Secondary effects by the topical corticosteroids treatment (TCS): epithelium atrophy is the main effect. Others can include telangiectasias and skin striae in the very short term (about two weeks) (12). Adrenal suppression or contact sensitivity, but with careful monitoring, these side-effects are rare (11).
- Sexual dysfunction and dyspareunia: may be attributed to different aspects. Firstly, skin is more sensitive and delicate which easily tears and can cause superficial dyspareunia. Thereupon, the fear of pain lowers sexual arousal, decreases lubrication and causes the pelvic muscles to contract. Finally, anatomical changes like hooding and burial of the clitoris, labial fusion and introital stenosis, may make intercourse painful or give rise to problems with achieving orgasms (28).
- Psychosexual impact; VLS does affect the psychological area and is an extremely distressing condition causing significant morbidity to those affected women (43). Dyspareunia and a negative female genital self-image (FGSIS) could lead to relationship breakdown. It could also lead to intimacy, sexual enjoyment or sexual intercourse avoidance, with a significantly less frequent sexual activity. There is also a negative correlation with sexual arousal, orgasm, and satisfaction rates with sexual activity (9). Therefore, impaired sexual function and relationship dissatisfaction can contribute to avoidance behaviour, depression, anxiety, low self-esteem and poor quality of life. This condition is a major motivation for surgical interventions (43).
- Impaired quality of life (QoL); women with LS experience frequent misdiagnosis or delayed diagnosis as a result of lack of knowledge by their healthcare professionals and this leaves women suffering from LS in search of answers and

support. Once they realize the impact of their disease on their lives, they experience many emotions (13) and many are concerned about how the disorder may progress (44). It is known that advanced disease severely affects the quality of life (5). With diagnoses, a profound impact on their quality of life starts. One of these areas is financial, because in many countries there is a lack of social health coverage and non-formulary treatments. Another area is the psychosocial participation and functioning where there is a reduced engagement in social activities. These women suffer from despair and mental anguish mostly, and also guilt, worry, embarrassment, and depression. The change in the female architecture can lead to create a feeling of loss of female identity. Another sphere is the worry about getting into any relationship or the loss of it because intimacy (with a partner or not) becomes impossible. Women affected from LS claim the need for knowledge, (for both parts, clinicians and patients) as far as financial, sexual and psychosocial concern too (13).

3.10 RISK OF MALIGNANCY

Vulvar squamous cell carcinoma (VSCC) is the fourth most common type of gynaecological cancer (approximately 3-5% of all gynaecological malignancies), and affects the external genitalia (45). According to different studies, during the past decades, the incidence rate of vulva cancer has been rising by 20% to 50%. The aetiology of VSCC is not fully known yet, but it seems that it can be attributed to human papilloma virus (HVP) and vulvar inflammatory conditions, like lichen sclerosus. What is known, is that the number of VSCC is higher in the elderly population (46).

At least 25% of VSCC can be attributed to human papilloma virus (HPV), especially type 16 (47), this is the HPV-induced or usual VIN (uVIN). Otherwise, approximately 60% of SCC is related to inflammatory dermatoses, such as LS, this is HPV-independent or differentiated VIN (dVIN) and has a high risk of malignant transformation (46) (32). So, both uVIN and dVIN are precursors of VSCC, but it is seen that dVIN associated with lichen sclerosus is more likely to be associated with a squamous cell carcinoma of the vulva than usual type VIN (uVIN) (9). However, the role of HPV as an oncogenic factor in LS diagnosed women is being discussed (10).

So, all studies agree that LS is associated with an increased risk of vulvar cancer, and what's more, P.Halonen et al., in a Finnish 2020 study, state that is also related to vaginal cancer, even if VLS characteristically does not affect the vagina (16). Thus, when we talk about vulva cancer

due to LS, we must distinguish between differentiated vulvar intraepithelial neoplasia (dVIN) and squamous cell carcinoma (SCC), where dVIN is the precursor lesion of SCC (or VSCC, used as a synonym in our project), especially the keratinizing type (9). dVIN is an uncommon variant of vulvar intraepithelial neoplasia (VIN) (47) (48), mostly seen in older women, that by histologic examination could seem banal, though it is a form of high-grade squamous dysplasia/carcinoma in situ according to the ISSVD.

dVIN is rarely an isolated discovery, and it is often identified in association with invasive VSCC or with a prior history of that (9) (45). dVIN has a significant under diagnosis (45). If we compare the diagnosis of uVIN and dVIN, the second one is less diagnosed as a solitary lesion and this can be due to:

a) dVIN clinical presentation is less characteristic (45).
b) Histopathological features overlap with other reactive disorders (45), so it can be a challenge to differentiate dVIN from LS even with histological biopsies (16).
c) The interval between uVIN and HPV-dependent VSCC is longer than dVIN and independent-HPV VSCC (46). This could be possibly due to the supposition that dVIN has a relatively brief intraepithelial phase before progressing to SCC (47).

It is generally supposed, then, that dVIN can develop from LS and the coexistence of both strongly increases the vulvar cancer risk. Some studies support this fact by the observation of both dVIN and LS adjacent to VSCC in 25-65% of cancer cases (49). dVIN should be suspected if there is any suspicious circumscribed lesion resisting to ultra-potent topical corticosteroids (UPTCS) (25).

Nevertheless, there is not sufficient data to show clear evidence of a causal association between VLS and neoplasia or a mere coexistence. Recent reports demonstrate a lower risk in women appropriately treated and under follow-up. Despite most cases of VIN will not develop into SCC, it is not possible to know which one will (9). However, if dVIN progresses into SCC, it has a high malignant potential (45) and tends to reoccur after excision (9) (25).

What is interesting, is the discussion about what increases more the risk of SCC development, the age at diagnosis of LS or the higher time of evolution of LS. Hedwig P. van de Nieuwnhof et al. state that the period of lichen sclerosus diagnosis was not associated with VSCC risk. What was seen was that the age at first LS diagnosis is linked with the prevalence and incidence of VSCC. In this way, the older the women were being diagnosed from LS, the more prevalent was

VSCC. So, maybe, and according to this study, there's no link between time evolution of LS and developing or not VSCC, but it exists between the age of LS diagnoses and development of VSCC (45). On the contrary, another study states that advanced disease severely affects an increased risk of vulvar squamous cell carcinoma (VSCC) (5). Also, Singh et al. describe that longer duration of symptoms and loss of vulvar architecture increase the risk of cancer, but they also state that women with LS-associated vulvar cancer are significantly older than women with LS alone (9). Recently, another study finds that different lengths of follow-up has an effect on the proportion of LS patients developing VSCC (16). Otherwise, most studies defend that in long-term evolution LS cases, a 4-5% of the women develop vulva cancer (6) (46).

According to our region of Terres de l'Ebre, although it has not been specifically analysed, our feeling shows the trend that those patients who are diagnosed at an earlier age, are the ones who have more risk of vulvar neoplasia.

So, as far as we are concerned, maybe a longer evolution of the condition increases the risk of cancer, but we aim that with this first step that our project represents, maybe we can extract some relevant information that can lead us to a conclusion, at least in our local population.

Differently, extra-genital LS is least suggested to be associated with malignant transformation (46) (31).

It is not likely that LS develops directly into cancer (9). Older studies talk about the evolution of LS to SCC, without a dVIN phase, where they supposed that LS with features such as parakeratosis, dyskeratosis, hyperplasia and basal cellular atypia had a higher risk of evolution into cancer (45), as well as with a longer lapse of time than the required from VIN to SCC (47). In 2011, van de Nieuwenhof et al. reassessed biopsies from previous years collected from 60 patients with the diagnosis of LS who later developed VSCC, and arrived at the hypothesis that some of the previous LS diagnoses might have actually been dVIN (45). According to current hypothesis, however, dVIN is considered to be the true precursor of vulvar SCC (16).

Up to now, we would like to empathize the importance of recognition of LS at risk of SCC development because the malignant potential of differentiated VIN is considered to be high and, therefore, would greatly help to select patients who need close follow-up as far as treatment differs between LS (topical superpotent corticosteroid ointment) and dVIN (surgical excision) (45).

The risk of malignancy is low if the LS has been diagnosed and treated early and appropriately, remains uncomplicated and it remains under control (6). Also, many studies have demonstrated that women who follow a compliant and optimal treatment modifies the course of the disease preventing scarring and also have lower rates of vulvar SCC to women who do not (8) (32).

To close this section, VLS predisposes a higher risk of cancer but not to a higher mortality (16) (5); even though, this last one is certainly raised when LS is concomitant with rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE) (16).

3.11 TREATMENT

The aim of the treatment is to, on the one hand, to minimize and control the symptoms, fundamentally pruritus and pain. On the other hand, to slow down the evolution of the disease and to prevent new lesions and sequels.

It is essential for patients to be counselled that LS is a chronic, relapsing and evolutive condition and therefore long-term treatment and follow-up is very important.

Also, they must be informed they have to make their own thorough explorations frequently in order to detect new lesions as early as possible (12) (32).

Patients should be made aware of the small risk of neoplastic change and, therefore, to contact their doctor if they notice a change in appearance (lump, ulceration or hardening of skin), or if symptoms change or worsen (7). Biopsy of such lesions will be important to exclude dVIN or invasive SCC (32).

There is a lack of randomized studies evaluating the different options of treatment. Additional research is needed to identify the optimal potency, dosing, and duration of use.

3.11.1 Topical Treatment

FIRST-LINE TREATMENT: TOPICAL CORTICOIDS

Nowadays, potent or ultra-potent topical corticosteroid (UPTC) are the first-line treatments recommended in Spanish, American and UK guidelines. Symptoms relief in 75-90% of patients, but, although spontaneous remission occurs, for most cases the treatment is lifelong (20).

Treatment of choice are UPTC like clobetasol propionate 0.05% or halobetasol 0.05%. Potent topical steroid like mometasone furoate 0.1% is a possible initial treatment too.

Mechanism of action

Corticoids are known for their anti-inflammatory effect. They promote: 1) inhibition oedema formation, 2) vasodilation reduction, 3) decreased migration of phagocytes to the area, 4) decreased fibrin and collagen deposits and 5) inhibition of keloid formation.

Reduction of flaking, itch and plaques formation is the clinical result of topical corticosteroids.

Adverse effects

They directly depend on the potency, duration of treatment and extension. They mostly occur in the non-LS affected vulva skin. These are cutaneous atrophy, telangiectasias and skin striae in the very short term (two weeks), mainly in the perianal area and hairy areas of the labia majora. The labia minora and clitoris are less susceptible to adverse effects (12).

Allergies to steroids of a topical preparation may occur after long-term use.

Monitoring, short-term treatment (not over 6 months) and low quantities can minimize them all.

Recommended regimen

Different regimens are used and are not well-stablished. What is common in almost every guideline, is that first of all, a continuous regimen is prescribed, then a de-escalation and finally a maintenance to fulfil the patient asymptomatic.

INITIAL THERAPY

The *Asociación Española de Patología Cervical i Colposcopia* (AEPCC) proposes two treatment plans, that can both be carried out:

1. **Continuous**: a nightly application for 6-12 weeks.
2. **De-escalation**: a nightly application for 4 weeks followed by one usage every 48 hours the following month, and finally 3 utilisations for week the last 4 weeks.

With 0.5gm in every utilisation is enough in both options. Ointment seems to reduce the irritation more than pomade.

Meanwhile, the European Guidelines propose these two different initial treatment options. The American College of Obstetricians and Gynaecologists (ACOG) follows the British Association of Dermatologists guideline, the second one in the following:

1. Once daily use of potent to ultra-potent topical steroids for 3 months.
2. Daily use for 1 month, then alternate days for 1 month and finally twice weekly for 1 month. Review at 3 months to assess response to therapy and to ensure proper applications.

In both cases, a twice daily application may occasionally be of additional benefit in resistant LS.

A second assessment 3 to 6 months later is reasonable for well-controlled patients.

MAINTENANCE THERAPY

Some patients will achieve remission for a long period of time, but not all of them, as some may be left with irreversible scarring. Yet, there is no way to know it at the moment of diagnosis.

With regard to *Asociación Española de Patología Cervical i Colposcopia* (AEPCC), maintenance therapy is based on the minimum dosage able to maintain the patient asymptomatic.

Once remission is achieved, AEPCC and ACOG recommend individualized long-term treatment, using a high or medium-high potency corticoid (MHPTC), e.g. mometasone furoate ointment 0.1%. The 2016 European Guideline for the management of vulval conditions recommends a twice-weekly application (0.5gm each usage).

Adverse effects such as atrophy, telangiectasia, striae or secondary infection due to long-term topical corticoids administration do not appear, as would be thought. It is secure in a long-term usage and may help to maintain normality skin colour and texture, prevent scarring and malignant change.

There is a debate and a lack of information or evidence if, either with remission of symptoms, patients should go ahead with topic treatment, because it is known that LS may progress and lead to more scarring (being the patient asymptomatic). In this case, lower potency corticoids

may be used, such as triamcinolone, betamethasone, fluocinolone, methylprednisolone, and dexamethasone.

TREATMENT FAILURE

If treatment with topical corticosteroids fails, the following steps should be (6) (7):

- Verify that LS diagnosis is correct. If not previously obtained, a biopsy should be performed.
- Check for treatment adherence: appropriate dosage and application to the correct site.
- Look for urinary incontinence, superimposed bacterial, viral (herpes simplex) or fungal infection (candidiasis), or the development of contact dermatitis (allergy to the medication) or lichen simplex chronicus. Exclude genital intraepithelial neoplasia. Although vitiligo does not cause any architectural change and is asymptomatic, it may coexist with LS, like psoriasis can also do.
- Consider vulvodynia if soreness becomes a predominant symptom rather than an itch.
- Even if improvement is not achieved with therapy and other causes have been ruled out, patients should be referred to a vulvar dermatoses specialist, who may prescribe alternative therapies (32).

The British Association of Dermatologists Guidelines for the management of lichen sclerosus 2018 recommends that in those patients resistant to topical corticosteroids and malignancy excluded by a biopsy, intralesional corticosteroid injections (triamcinolone) can be considered. There is no consensus on repeated injections.

SECOND LINE TREATMENT: TOPICAL CALCINEURIN INHIBITORS

Tacrolimus and pimecrolimus are low anti-inflammatory action drugs, local immunomodulate and low immunosuppressant systemic effect (12). Otherwise, they are not licensed for the treatment of LS. Comparing pimecrolimus 1% cream and clobetasol propionate 0.05% cream, clobetasol was found to be superior in improving inflammation (7).

They are recommended for those patients resistant to topical or intralesional corticosteroids or are at risk of skin atrophy (6).

Adverse effects

Burning sensation is the principal cause of abandon (6). Local irritation is the other main adverse effect (7). It is not recommended in long-term therapy, because, although the relationship has not been proven, the Food and Drug Administration (FDA) has warned about the potential risk of other localizations cancer (12) (6).

EMOLLIENTS

Topical emollients (creams or oils) create a protective barrier and prevent from cutaneous dehydration, and therefore, they may give symptom relief after initial steroid treatment. They can be used when necessary (if there is good response to TCS) and there are no adverse effects described (7) (12).

3.11.2 Excisional Treatment

Consists of removing the lesion totally or partially.

It is not indicated as a first-line treatment, because of its low efficacy and inner complications. Its indications are basically three:

- Severe morphology distortions of the vulva secondary to sclerosis, scarring and introitus narrowing. The aim is to restore architecture and function of the vulva. This procedure can be performed with CO_2 laser. Monitorization after surgery is so important and vital. It can be necessary to use vaginal dilation and UPTC in order to avoid recurring introitus stenosis or skin retraction.
- Clitoral fusion: only in rare situations (e.g. severe problems with self-esteem, sexual function or urination). There is a chance of recurrence after surgery.
- dVIN or suspected VSCC coexistence.

We would like to sum up the treatment with the adapted algorithm of the *Asociación Española de Patología Cervical i Colposcopia* (AEPCC) guidelines (Fig. 12) (12) Annex 5).

3.11.3 Other Treatment Options

There is a lack of published evidence. Most of them are practically in the field of research and their clinical use is limited.

Dynamic phototherapy, ultraviolet A1 phototherapy, systemic retinoids, CO_2 laser vaporization, cryotherapy, oral and topical cyclosporine, oral methotrexate, or, experimentally, injection of adipose tissue stromal vascular fraction with stem cells or platelet rich plasma.

3.12 PROGNOSIS AND MORTALITY

We would like to emphasize that lichen sclerosus is a chronic disease with a relapsing course. Therefore, affected women will need a long-term follow-up and most frequently with a long-term treatment plan with different options. We would also like to remember that their quality of life can be really impaired.

Mortality is linked with vulvar cancer development (5) (16). According to the *National Cancer Institute*, the 5-year relative survival of vulva cancer is 70.4% (data from 2010 to 2016) (50).

3.13 FOLLOW-UP

LS is a chronic and inflammatory dermatosis normally with a fluctuant course with periods of worsening and recurrence of the symptoms. So, the reasons why it is important to follow up are to assess response to treatment (in order to change or not the treatment plan), to confirm good control of the disease and to check for complications. It is also an opportunity to provide patient education and to ensure that patients know how to manage their disease well. The frequency and length of follow-up must be tailored to the patient (6).

If their disease is not controlled, then there is the risk of developing differentiated vulvar intraepithelial neoplasia (dVIN) and a potential risk of evolving to vulva cancer. As we have already said above, dVIN has a higher malignant and progression potential to squamous cell carcinoma (SCC), more than the VIN associated with HPV.

That is why we insist on an early diagnosis, treatment and an adequate follow up is so important. It is recommended to be performed in the gynaecology and dermatology units (12).

The AEPCC recommends a follow up in the following situations:

- Non-controlled symptomatology despite topical treatment with corticoids applied 3 times per week for 3-6 months.
- Patients with hyperkeratotic plaques and/or localized skin lesions that do not respond to traction, or areas of VIN type differentiation or invasive injury. In these cases, a vulvar biopsy will be indicated or repeated.
- Patients with a history of dVIN or invasive lesions.

The *2014 UK National Guideline on the Management of Vulval Conditions* (27) and the *2016 European Guideline for the management of vulval conditions* (7) recommend this follow-up:

- Assess response to treatment after three months. Also check that the patient is using the topical corticosteroid appropriately (6).
- Stable disease should be reviewed annually, and this can be done by the general practitioner (GP) in those patients with well-controlled disease. This must be communicated to the patient and GP by the clinic.
- Patients should be informed that if they notice the development of a lump, sore area, change in symptoms or change in appearance, they should ask for a medical review.

More recently, the *British Association of Dermatologists 2018 Guidelines for the management of lichen sclerosus* (6) have done more specific recommendations for adult female patients. We only note the differences with the recommendations above.

1. If the course is uncomplicated and responds to topical treatment, they need limited follow-up:
    - One at 3 months
    - Another 6 months later to ensure that the patient is treating herself and resolve any doubts before discharging to the care of her primary physician. If she needs a continued topical treatment whereas with corticoids, it is suggested that they see their primary-care physician once a year; If she needs continued emollients without corticoids, then, there is no need.
2. In the case of low or non-response to topical treatment, worsening of symptoms, atypical course, uncertainty about intraepithelial neoplasia or previous cancer or any type of VIN, then long-term follow-up with a specialist is appropriate.
3. Patients with severe fusion who require surgery will need close follow-up postoperatively and also intensive topical steroid treatment to prevent recurrence of fusion.

4 JUSTIFICATION

This is an initial study where we would like to see the clinical and sociodemographic profile of female patients diagnosed with vulvar lichen sclerosus in the region of Terres de l'Ebre. This is the first study of this kind of disease in this region. From that, if one or more characteristics compiled in our study seem to be a risk factor for the development of the condition, at least in our region, we would like to propose a second project in order to evaluate it further. Also, as vulvar lichen sclerosus is a chronic and low-quality life related condition, in our opinion, it would be interesting to know more about how the disease affects our patients; so we can offer a better medical and non-medical attention and they would be able to achieve a better life quality and the most optimal treatment they need.

What's more, there are some very recent studies evaluating new promising treatments such as micro-ablative CO_2, ultrasound therapy, stromal vascular fraction enriched fat grafting, platelet rich plasma, fat-derived mesenchymal cells, etc. We know we are dealing with a disease without a cure, with a long-term treatment needed and with many failures. We consider it important to know the needs of our patients for a new treatment, in order to evaluate these needs from a medical, economical and quality life points of view, to start the development of this new treatment.

5 HYPOTHESIS

To realise that some of the sociodemographic and clinical characteristics collected in our study sample are present in the majority of it. Therefore, one or more items could be a possible risk factor for the development of vulvar lichen sclerosus in our sample and, consequently, in our female population.

6 OBJECTIVES

6.1 MAIN OBJECTIVE

To know the clinical and demographic profile of women diagnosed with vulvar lichen slcerosus (VLS) in the region of Terres de l'Ebre.

6.2 SECONDARY OBJECTIVES

- To determine the prevalence and incidence of women with vulvar lichen slcerosus (VLS) in the region of Terres de l'Ebre.
- If the hypothesis is accomplished, to suggest carrying on a study for the purpose of determining a risk factor in our female population really exists.

7 METHODOLOGY

7.1 STUDY DESIGN

This study is designed as an observational, descriptive, population and transversal study. It will be multi-centric though it will include all the medical centres with gynaecological assistance belonging to *Institut Català de la Salut* (ICS) in the region of Terres de l'Ebre, where the hospital of reference is Hospital de Tortosa Verge de la Cinta (HTVC). It will be carried out from March 2021 to March 2025. There will not be a patient follow-up. Therefore, we are going to collect the information only once per individual during the study and the analysis will be retrospective.

The medical centres with gynaecological assistance cited are:

- Baix Ebre: ABS Ametlla - Perelló, ABS Tortosa -Est, ABS Tortosa -Oest, ABS Aldea - Camarles - Ampolla, ABS Deltebre, ASSIR CAP Baix Ebre, Hospital Verge de la Cinta de Tortosa.
- Montsià: ABS Ulldecona - La Sènia, ABS Amposta, ABS Sant Carles - Alcanar.
- Terra Alta: ABS Terra Alta.
- Ribera d'Ebre: ABS Flix, ABS Móra La Nova - Móra d'Ebre.

7.2 STUDY POPULATION

The population in this study will include all women suffering from vulvar lichen sclerosus (VLS) clinically and pathologically diagnosed controlled in the different medical centres belonging to Institut Català de la Salut (ICS) in the region of Terres de l'Ebre between March 2021 and March 2025.

7.2.1 Inclusion Criteria

To participate in the study individuals must meet all of the criteria of inclusion:

- Women suffering from vulvar lichen sclerosus (VLS) with clinical and histological diagnosis.
- Participants are willing and able to give informed consent for participation in the study.
- Mentally and/or physically able to complete all study questionnaire and scores.
- Patients who had completed all study questionnaire and scores.
- Patients older than 18 years old.

7.2.2 Exclusion Criteria

Individuals will not be able to participate in the study if any of the following criteria is met:

- Women with any other vulvar disease that is not VLS.
- Women with only clinical or only histological VLS diagnosis.
- Patients who do not give their informed consent.
- Patients who had not completed all study questionnaire and scores.
- Patients younger than 18 years old.

7.3 SAMPLE

7.3.1 Sample Selection

Participants will be selected in their follow up visits with their midwife or gynaecologist who work in the *Institut Català de la Salut* (ICS) medical centres cited below. The selection will be done following the non-probabilistic consecutive model. Patients will be chosen applying the inclusion and exclusion criteria mentioned. They will be orally informed of the study objective and then given the information document of the study (Annex 6). After receiving the information, those who want to participate in the study will be given the informed consent form (Annex 7) and, when signed, individuals will be enrolled in the study.

7.3.2 Sample Size

It is a population study without a specific control group, and we will not compare variables. Our sample includes all women who accomplishes de inclusion criteria.

First step it has been to calculate how many women over 18 years old are in the region; this has been possible with the IDESCAT 2019 population information (51) (Annex 8).

A random sample of 282 individuals is sufficient to estimate, with 95% confidence and an accuracy of +/- 2 percentage units, a population percentage that is expected to be around 3%. The percentage of replacements required is expected to be 1%.

As it is a population study, we have considered that 30 patients per year it would be statistically significative.

Our clinical experience is that we visit about 10 VLS patients every month. In this way, we estimate 28,2 months (we have approximated to 29 months) required for the patient recruitment.

7.4 VARIABLES AND METHODS OF MEASURAMENT

We have 46 variables in order to define as beast as possible the profile of our sample. They are collected in two questionnaires (one for the patient and one for the General coordinator) (Annex 9). We have used three scores in order to determine three of the variables: the sexual function variable has been collected with The Female Genital Self-Image Scale (FGSIS) (Annex 10), the quality of life variable has been collected with the Dermatology Life Quality Index DLQI score (Annex 11) and the severity of the condition variable has been collected with the Clinical Scoring System for Vulvar Lichen Sclerosus (CSS) (Annex 12). Due to this study being transversal, where we want to determine the clinical and demographic profile of our patients, there are not dependent variables, independent variables nor covariables.

Before starting with the definition of the variables, we would like to explain why we have chosen these scores and not others. There is a wide variation in measurement of sexual function, severity and quality of life in lichen sclerosus among clinical studies, though it is very difficult to compare between them. An amount of scores exists that have been used in different studies. Some of them are not validated for lichen sclerosus and furthermore some clinical studies about treatments for LS did not use any validated score and they used their own created scale. After a long extensive review, we decided to include these 3 scores or scales tools in our study. All of them were free of charge.

7.4.1 Study Variables

7.4.1.1 Variables collected from the patients' questionnaire

1. **Age of the patient:** It will be expressed by years as a continuous quantitative variable.
2. **Socioeconomic status.** Defined as 3 ordinal qualitative variable based on the *Enquesta de Salut de Catalunya* (ESCA) (52). The possible answers will be classified by:
   - **Educational level**: no studies or primary studies only, secondary studies, university degree.
   - **Social class**: class I (managers, university professionals, directors), class II (intermediate occupations, self-employed workers), class III (manual workers) and NS (unclassifiable).
   - **Employment situation**: housework, unemployed, active worker.
3. **Relationship status:** defined as a nominal qualitative variable. The possible answers will include: single, married, judicially separated, divorced, widowed, current partner

(defined as well-stablished partner/s according to the patient criteria) and "I prefer not to answer".

4. **Smoking.** Defined as a nominal qualitative variable and will be defined as: never smoked (those who have never smoked), ex-smoker (not currently smoking, >1 year without smoking) or smoker (at least one cigarette during the course of the last year).
5. **Amount of tobacco.** Defined as continuous quantitative variable. If the patient is defined as a smoker in the previous variable, we would like to add its measure by the formula *packets of cigarettes/year*, which will be calculated by multiplying the number of packets of cigarettes smoked per day by the number of years the person has smoked.
6. **Drugs usage**. It will be expressed by "**yes**" or "**not**" and defined as a dichotomous nominal qualitative variable (drug use over the last year / no drug use over the last year). The possible answers will include: alcohol, cannabis, cocaine, opiates, amphetamines and heroine.
7. **Frequency of drug usage.** Defined as an ordinal qualitative variable. It will be responded in case of any of the previous answers is "**yes**". The possible answers will include: absence of drug use, daily use, once a week use, once a month use and once a year use. It evaluates alcohol, cannabis, cocaine, opiates, amphetamines and heroine.
8. **Onset of the VLS.** It will be expressed by years as a continuous quantitative variable.
9. **Current treatment.** It will be expressed by "**yes"** or "**no"** as a dichotomous nominal qualitative variable. We will define "yes" as if the patient has done any treatment during the course of the last year.
10. **Type of current treatment.** It will be expressed by "**yes"** or "**no"** as a dichotomous nominal qualitative variable. It will be responded in case if the previous answer is "**yes**". We will define current as the treatment/s done during the course of the last year. The possible answers will be classified by clobetasol propionate 0.05% (and its different commercial nouns), halobetasol 0.05% (and a commercial noun), mometasone furoate 0.1% (and its different commercial nouns), tacrolimus (and a commercial noun), pimecrolimus (and its different commercial nouns), emollients, methylprednisolon aceponate 0,1% (and a commercial noun) and excisional treatment (surgical treatment).
11. **Other treatment options.** It will be expressed by "**yes"** or "**no"** and defined as a dichotomous nominal qualitative variable. The possible options will include: vulvoperineoplasty, topical retinoids and systemic retinoids. We have decided to include these ones because they correspond to the last line treatment. We will define it as if the patient had the necessity of one or more of these treatment/s along the course of their condition.

12. **Necessity of a treatment change.** It will be expressed by "**yes"** or "**no"** and defined as a dichotomous nominal qualitative variable. We will define it as if the patient had the necessity to change one or more treatment/s along the course of their condition.
13. **Reason of the treatment change.** It will be expressed by "**yes"** or "**no"** and defined as a dichotomous nominal qualitative variable. It will be responded in case if the previous answer is "**yes**". The possible answers will be classified by adverse reaction, secondary infection and not improvement of the symptoms despite a correct treatment.
14. **Time without symptoms**. It will be expressed by months as a continuous quantitative variable. We will define it as the months the patient have not felt any symptom from the last satisfactory treatment they have done or the current treatment they are doing until the day of the data collection.
15. **Relapses**. It will be defined as a discrete quantitative variable. Defined as the number of times that the patient has needed to start again with any treatment after finishing a satisfactory treatment plan along the course of their condition.
16. **Follow-up care**: It will be expressed by "**yes"** or "**none"** and defined as a dichotomous nominal qualitative variable. We will define the answer "yes" as at least one visit per year from their diagnosis.
17. **Follow-up care specialist**. It will be expressed by "**yes"** or "**no"** and defined as a dichotomous nominal qualitative variable. We have included all the specialists who attend VLS. The possible answers will be: primary care practitioner, gynaecologist and dermatologist. The previous answer nor the frequency of visits in a period of time matter for answering this variable.
18. **Family history of genital LS (male and/or female relatives):** It will be expressed by "**yes"** or "**no"** and defined as a dichotomous nominal qualitative variable. We will include as a "yes" either they are alive or not.
19. **Relation to the affected relative**. It will be expressed by "**yes"** or "**no"** and defined as a dichotomous nominal qualitative variable. It will be responded in case the previous answer is "**yes**". The possible answers will include: 1st degree, 2nd degree and 3rd degree. We include these degrees of kinship because regarding to the bibliography, most of the relatives are first degree.
20. **Daily vulvar hygiene.** It will be expressed by "**yes"** or "**no"** and defined as a dichotomous nominal qualitative variable. We will define this variable as the daily cleanliness of the vulva with any type of soap currently.

21. **Usage of a specific soap ("intimate gel").** It will be expressed by "**yes"** or "**no"** and defined as a nominal dichotomous qualitative variable. The previous answer nor the frequency of vulvar hygiene matter for answering this variable.
22. **Birth given**. It will be expressed by "**yes"** or "**none"** (as a synonym of nulliparity) and defined as a dichotomous nominal qualitative variable.
23. **Number of vaginal labours.** It will be expressed in numbers and defined as a discrete quantitative variable. It will be responded in case the previous answer is "**yes**".
24. **Instrumental delivery**. It will be expressed by "**yes"** or "**no"** and defined as a nominal dichotomous qualitative variable. It will be responded in case the answer in "number of vaginal labours" is one or more. We will include as instrumentation the usage of forceps, suction pad or spatulas and so the answer will be "yes".
25. **Performance of episiotomy in delivery.** It will be expressed by "**yes"** or "**no"** and defined as a nominal dichotomous qualitative variable. It will be responded in case the answer in "number of vaginal labours" is one or more.
26. **Number of caesarean births**. It will be expressed in numbers and defined as a discrete quantitative variable. It will be responded in case the "birth given" variable answer is "yes".
27. **Breastfeeding**. It will be expressed by "**yes** or "**no"** and defined as a dichotomous nominal qualitative variable. It will be responded in case the "birth given" variable answer is "yes". We will define it as any amount of time of breastfeeding in any amount of babies.
28. **State of menopause**. It will be expressed by "**yes** or "**no"** and defined as a dichotomous nominal qualitative variable. It will be expressed by two states: pre-menopause or peri-menopause (we will define it as the time before the last date of the period) and post-menopause (we will define it as the time after the last date of the period).
29. **Years from the post-menopause**. It will be expressed by years and defined as a continuous quantitative variable. It will be responded if the answer to the previous question is "yes" to "post-menopause" option.
30. **Usage of contraceptive method/s**. It will be expressed by "**yes"** or "**no"** and defined as a dichotomous nominal qualitative variable. We define "yes" as the usage of any amount or type of contraceptive method over the last year.
31. **Type of contraceptive method/s used**. It will be expressed by "**yes"** or "**no"** and defined as a dichotomous nominal qualitative variable. It will be responded if the answer to the previous question is "**yes**". We will define this variable as the type or types of contraceptive methods/s used during the course of the last year. The possible answers

will be: caps or diaphragms, combined pill, female condom, male condom, contraceptive implant, contraceptive injection, contraceptive patch, IUD (intrauterine device or coil), IUS (intrauterine system or hormonal coil), natural family planning (fertility awareness), progestogen-only pill, vaginal ring, female sterilisation and male sterilisation (vasectomy).

32. **Sexual orientation**. Defined as a nominal qualitative variable. The possible answers will be: heterosexual/straight, homosexual/lesbian, bisexual, questioning or uncertain, asexual and "I prefer not to answer".
33. **Type of sexual activity over the last year**. Defined as a nominal qualitative variable. The possible answers will be: vaginal intercourse, anal intercourse, masturbation, oral sex, none of them and "I prefer not to answer".
34. **Number of sexual partners during patient's life**. It will be expressed by numbers and defined as a discrete quantitative variable. There will be an extra option of "I prefer not to answer".
35. **Sexual function.** We will use The Female Genital Self-Image Scale (FGSIS) (Annex 10) in order to define this variable. This scale enables a more objective assessment of female genital self-image status and is based on women's experience of orgasm. It is self-explanatory and can be simply handed to the patient who is asked to fill it in without the need for detailed explanation. FGSIS is a 7-item brief (generally completed in <5 minutes) questionnaire.

    Answers are scored on a 1 to 4-point response scale ("strongly dis-agree" [1 point], "disagree" [2 points], "agree" [3 points], or "strongly agree" [4 points]). An individual's total score is obtained by adding the scores of the 7 answers and can range from 7 to 28. A lower score indicates a negative genital self-image. It will be defined as discrete quantitative variable.
36. **Quality of life.** We will use the Dermatology Life Quality Index (DLQI) score (Annex 11) in order to define this variable. DLQI is an adult-designed questionnaire that assess the implication of the dermatology disease at issue in different psychosocial situations. It is self-explanatory and can be simply handed to the patient who is asked to fill it in without the need for detailed explanation. It is usually completed in 1-2 minutes.

    DLQI is composed of ten questions with four possible answers ("not at all", "a little", "a lot" and "very much"). An extra answer is included if the patient considers the question is not relevant.

    Answers are rated from 0 ("not at all") to 3 points ("very much"); "not relevant" response is also rated as 0 points. Thus, possible results scores range from 0 (no effect

at all on patient's life) to 30 (extremely large effect on patient's life and therefore the greater the impairment of quality of life (QoL)). It will be defined as discrete quantitative variable.

7.4.1.2 Variables collected from the General coordinator's questionnaire

37. **Race**. Defined as a nominal qualitative variable. The possible answers will be: Hispanic/Latino, American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, and Two or more races.
38. **Drug allergies**. Defined as a nominal qualitative variable. We will only include those which are registered in the SAP/ECAP.
39. **Body mass index (BMI):** we will treat the BMI like an ordinal qualitative variable, divided into 4 groups:
    - < 18,5 kg/m^2 → low weight
    - 18,5-24,9 kg/m^2 → normal weight
    - 25-29,9 kg/m^2 → overweight
    - ≥ 30 kg/m^2 → obesity

The BMI will be collected from the medical history from SAP/ECAP and if we do not have the data or the necessary information to calculate it, then we will run the exploration in order to obtain it. BMI will be calculated by the formula: BMI = weight (Kg)/height^2. It is important that the patient is wearing light clothing and no shoes.

40. **Other vulvar dermatoses.** It will be expressed by "**yes"** or "**no"** and defined as a dichotomous nominal qualitative variable. We will only include those which have been diagnosticated by a doctor and registered in the SAP/ECAP along their life. We have included those which are explained in the bibliography. The possible answers will be: lichen planus (LP), localized scleroderma and morphea.
41. **Concomitant dysplasia or neoplasm.** It will be expressed by "**yes"** or "**no"** and defined as a dichotomous nominal qualitative variable. We will only include those which have been diagnosticated by a doctor and registered in the SAP/ECAP along their condition. We have included those which are explained in the bibliography; the possible answers will be: differentiated vulvar intraepithelial neoplasia (dVIN) and squamous cell carcinoma (SCC).

42. **Current or past infections**. Defined as a nominal qualitative variable. We will only include those which have been diagnosticated by a doctor and registered in the SAP/ECAP along their life. We have included those which are explained in the bibliography. The possible answers will be HPV, EBV, HCV, herpes virus, *Streptococcus*, *Borrelia burdogferi* and candidiasis.
43. **Associated comorbidities or diseases**. It will be expressed by "**yes"** or "**no"** and defined as a dichotomous nominal qualitative variable. We will only include those which have been diagnosticated by a doctor and registered in the SAP/ECAP along their life. We have included those who are explained in the bibliography. We will classify the comorbidities by: Hashimoto thyroiditis, Graves' disease, alopecia areata, vitiligo, pernicious anaemia, Systemic lupus erythematous (SLE), diabetes mellitus (DM) and celiac disease.
44. **Extra-genital LS affection.** It will be expressed by "**yes"** or "**no"** and defined as a dichotomous nominal qualitative variable. We will only include if it has been diagnosticated by a doctor and registered in the SAP/ECAP along their life.
45. **Reason of menopause**. It will be expressed by "**yes** or "**no"** and defined as a dichotomous nominal qualitative variable. It will be responded if the patient is in the state of post-menopause. The possible answers will include: physiological (defined as non chemical and non surgical) chemical and surgical.
46. **Severity of the condition** We will use the Clinical Scoring System for Vulvar Lichen Sclerosus (CSS) score (Annex 12) in order to define this variable. This a physician-administered clinical score useful for assessing impression of the severity of the condition (which is our aim with this score), treatment response over time and ease diagnosis of VLS too. The estimated time that it takes the gynaecologist to collect this data is approximately 5 minutes. It will be defined as discrete quantitative variable.

    There are six items considered: erosions, hyperkeratosis, fissures, agglutination, stenosis, and atrophy. Each item is scored on a three-point Likert scale ranging from 0 to 2, with 0 representing "normal findings", 1 "moderate changes", and 2 "severe changes". The range of the physician-administered score is therefore 0 at minimum and 12 at maximum in total. In the presence of typical symptoms, the diagnosis of LS can be established with clinical confidence using a cut-off value of 4.

    - Erosions: grade 1 erosions (moderate) are defined by 1–2 small erosions, almost not macroscopically visible and grade 2 (sever) erosions are defined by macroscopically visible and/or more than 2 or confluent lesions.

- Hyperkeratosis: grade 1 (moderate) is defined by affecting the vulva and perineum up to 10% and grade 2 (sever) by more than 10%.
- Fissures: grade 1 (moderate) fissures are defined by rhagades affecting the posterior introitus, grade 2 (sever) by generalized vulvar rhagades.
- Agglutination grade 1 (moderate) is defined by partially affecting the preputium clitoridis and the labia minora, grade 2 (sever) by complete agglutination of both.
- Stenosis grade 1 (moderate) mean a narrowing of the introitus, which could still be passed by two fingers, grade 2 (sever) a narrowing which could be passed by less than two fingers.
- Atrophy grade 1 (moderate) is defined by shrinkage of small labia and clitoris; in grade 2 (sever) atrophy labia minora and clitoris are no longer visible.

7.4.2 Data Collection

Before starting the study, we will assign a General coordinator (principal investigator) in order to be in charge of acquiring and registering all the variables. Afterwards, data will be reported and evaluated by a Statistics analyst to a database specifically designed for the study.

Participants will be selected by a non-probabilistic consecutive model, following the inclusion and exclusion criteria in the different public medical centres belonging to ICS.

The planning will consist of an organization of the gynaecologist visits in the different medical centres mentioned before in order to that the General coordinator can attend every centre on the day that there is gynaecologist consulting.

In our opinion, it is important that someone, the GC in this case, be there during the process in case they have some questions about the questionnaire or scores.

For our project, we will need two questionnaires (one for the patient and one for the GC) (Annex 9) and three scores in order to complete the data collection. The patient's questionnaire consists of 5 sections and the GC's questionnaire consists of 4 sections (responding to information of the patient's medical records). The FGSIS (Annex 10) score and the DLQI (Annex 11) score will be completed by the patient and the CSS (Annex 12) score will be completed by the attendant gynaecologist or midwife. All the data collection (including the scores) can be answered in approximately 40 minutes.

Initially, the midwife or gynaecologist will select the patients who fulfil the inclusion and exclusion criteria. They will explain this project to these patients and ask them if they would like to participate in the study. If they give their verbal agreement, they will be referred to an office in the same centre after their visit. There, the General coordinator will read and give them the information sheet (Annex 6) and both patient and main investigator (General coordinator) will sign the informed consent (Annex 7). Afterwards, the General coordinator, in the presence of the patient can be completing the GC's questionnaire with the information from the patient's medical records. So, this will create more efficiency and accuracy while gathering all the information about the patient's medical history. The patient, at the same time, have to fill in the patient's questionnaire and note the two scores (FGSIS and DLQI). If some of the information needed is not in the patient's medical records at the time of entering the study, a review of the information must be made, and complete all the information if necessary, at the time of consultation. Data from the recent visit will also be collected from the SAP or ECAP. If the information related to BMI and extra-genital affection is not available in the medical record, a physical examination will need to be assessed by a doctor or a nurse. Therefore, the medical centre must be equipped with a weighing platform and a measuring system. The CSS score will be filled in by the attending gynaecologist or midwife when the informed consent is signed.

Every time a patient with a possible diagnosis of VLS presents themselves, they will be informed of the study and that, if the patient finally accomplishes the diagnoses and the inclusion criteria, they are invited to enrol and participate in our project.

If the collected information is not completed, or if there is an error or we need a clarification, we will do it by way of a phone call. In the case of receiving an insufficient amount of answers we will send a reminder to the participant by the same way.

8 STATISTICAL ANALYSES

Statistical analysis will be performed using Statistical Package for Social Sciences (SPSS) software:

8.1 UNIVARIATE ANALYSIS

In the univariate analysis, variables will be defined as qualitative (categorical) or quantitative variables:

- For qualitative variables, the results will be expressed in percentages, proportions or frequencies with confidence intervals of 95%.
- For quantitative variables, being either continuous or discrete, we will determine if they follow a normal distribution or not by using a histogram. We will use mean ± standard derivation (when they follow a symmetric distribution) or median and interquartile range (when they follow an asymmetric distribution).

9 ETHICAL CONSIDERATIONS AND LEGAL ASPECTS

This protocol will be presented and submitted for consideration, evaluation and approval by the Clinical Research Ethics Committee (CEIC) of Hospital de Tortosa Verge de la Cinta (HTVC) as the coordinating study centre. The Committee will ensure that the protocol fits the ethical requirements for being approved. In the case of the CEIC having objections, they will be considered, introduced and modified. Management's Department authorization of all the medical centres enrolling in the study will also be required.

The study will be performed under the requirements expressed in the *Declaration of Helsinki of Ethical Principles for Medical Research Involving Human Subjects* signed by the World Health Association in October 2013, the *Principles of Biomedical Ethics* from Beauchamp and Childress (*Principle of respect for autonomy, Principle of nonmaleficence, Principle of beneficence, and Principle of justice*) from 1970 and reviewed in 2009, and to *Orden Ministerial order* SAS/3470/2009 defined in the current legislation in Spain related to the conduct of observational studies in order to ensure the human rights and ethical principles are being adhered to.

In order to enrol the study, patients will have to voluntarily sign the informed consent (Annex 7). Therefore, before being included in the study, all participants will be appropriately informed and will be given an information sheet in an understandable language for them (Annex 6). An identification number will be used in the database elaboration instead of the patient's name. Participants will have the right to access, modify, oppose or remove their personal data, as well as to withdraw their consent without any negative effect on their relationship with their assigned doctor or treatment received once the study has started. So that participants' autonomy will be respected during the whole process, according to the *Ley 41/2002, de 14 de noviembre, básica reguladora de la autonomía del paciente y de derechos y obligaciones en materia de información y documentación clínica* and the basic ethical principle of autonomy.

The processing of personal data required in this study, the personal data cession of all the patients and their confidentiality and communication will obey the *Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation) and the Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y Garantía de los derechos digitales and*

the Real Decreto 1720/2007, de 21 de diciembre por el que se aprueba el Reglamento de desarrollo de la Ley Orgánica 15/1999.

Therefore, this study guarantees the confidentiality and anonymity of all data related to the participants and exclusively used for the purpose of the research. The data access will only be available to the research team. The access to this information by a third person will not be allowed.

Each person on the research team and the hospital management must sign a statement attesting to having read and approved the final protocol and agree with the national and international aspects of research.

The research team declares to have no conflicts of interest with any party or organ related to this study. They will have to agree to publish all data and results with clarity and transparency, and they will not exclude unfavourable events or data.

10 STUDY LIMITATIONS – STRENGHTS AND WEAKNESSES

Related to the study design

As a transversal study, it leads us to suggest a hypothesis. On the contrary, we cannot get any causality or event sequence. This is why we would propose a further study if a hypothesis of a possible risk factor appears.

Related to the sampling

Since the study will use a consecutive sampling, a great emphasis must be put within Gynaecologist Department to avoid forgetting to enter any patient in the study. Moreover, it is a non-probabilistic sampling. Thus, it may affect the external validity of the study.

VLS is a low prevalent and incident disease, so the time of recruitment of the patients could be higher than expected, which would lengthen the duration of the study. Nevertheless, VLS patients normally have a close follow-up, so we do not expect the time of the study to lengthen. Low prevalence and incidence could make it difficult to extrapolate to other regions or countries. What is more, low patient recruitment is a limitation that we should consider. The main reason could be either the improvement of symptoms (patients do not come to the appointment) or the lack of improvement after many changes in the treatment (patients decide to change their doctor, or they just stop visiting). On the other hand, woman may be more likely to seek gynaecologic care if they have symptoms.

Otherwise, and as mentioned, this is a multi-centric study, and this allows us to have a higher sample.

Related to data collection

The collection of data is extensive (about 40 minutes), and this could lead to incomplete or inaccuracy data collection. Also, the patient may not remember (memory bias), or we could find a lack of information in the medical history.

Even if analysis will be performed by the same Statistics analyst, the risk of information bias still exists. In order to avoid it, the Statistics analyst will use the same criteria in all situations to ensure equality.

We are not going to need any laboratory or expensive material support. Therefore, our budget will not be very costly.

Related to inter-explorer differences

None of our centres are a vulvar disease referral centre.

This study is multi-centric and therefore patients will be assessed in different medical centres belonging to ICS around Terres de l'Ebre. In this way, many different gynaecologists will carry out the exploration. Although CSS scale, in our opinion well defined, is still observer – dependent and differences may appear when taking the results. So, before starting the study, different meetings will be arranged in order to make sure everybody understands the procedure and which parameters they have to take into account. If necessary, we could also impart a seminar in order to form all the medical personnel in exploring VLS in order to decrease differences in the results. Each medical centre will be able to be in contact with the research team during the recruitment and data collection. Also, being a multi-centric study, this could make the results more generalizable.

11 FEASABILITY

Gynaecologists and midwives performing the study are used to treating gynaecological pathology and, if needed, a special training on VLS will be performed. They will combine their healthcare work with the active participation of this study, at no additional cost.

It will be easy to organize meetings in Tortosa as the centre coordinating the study.

As it is a multi-centric study, patients' recruitment will be in less time and so, we can reduce data collection length. Also, this provides us having a larger coverage of the area. We expect to have enough patients to recruit (we need a total of 282) in a period of 4 years, taking into consideration the number of patients seen each year.

All of the medical centres involved are equipped with competent medical staff and adequate technological resources sufficient to accomplish the objectives of the trial.

A General coordinator will be hired to coordinate and control data quality, due to the fact that this multi-centric study comprises many medical centres and there must be an extra effort or reinforcement on these aspects to avoid rectifiable errors than can reduce easily the value of the study. We will hire a Statistics analyst, as well as, to process the statistical analysis implicated.

We expect that the budget will not create a barrier to the development of this project as it has been adjusted as much as possible. The research team is putting a lot of effort in funding this project by way of public money.

Because of our intense investigation of this topic, we consider this study to be feasible regarding the sample size and availability, the multi-centric character, the estimated time and budget and the professionals involved.

12 WORK PLAN

The duration of the study is estimated in 4 years from March 2021 to March 2025 and it is divided into 8 stages as described below.

12.1 RESEARCH TEAM PERSONNEL

The research team will be composed by:

- 1 General coordinator (GC)
- Gynaecologists and midwives that work in health care centres belonging to ICS and are willing to participate. The hospital of reference is *Hospital de Tortosa Verge de la Cinta* (HTVC).
- 1 Statistics analyst (SA)

12.2 STAGES OF THE STUDY

The research will include the following stages:

12.2.1 STAGE 0: Protocol Design and Protocol Development (March 2021- June 2021)

- Development of the hypothesis and delimitation of the objectives will be defined by the clinical needs and the current bibliography.
- A review about vulvar lichen sclerosus (VLS).
- Protocol design and writing.
- Determination of the collaborating professionals in the study.

12.2.2 STAGE 1: Acceptance (July 2021 – September 2021)

Presentation to Clinical Research Ethical Committee (CEIC, "Comitè Ètic d'Investigació Clínica") of HTVC. The GC will be responsible to present the current protocol to the CEIC of HTVC. Any objection given by the CEIC will be considered, revised and modified in the protocol.

12.2.3 STAGE 2: Coordination and Organization (October 2021 - November 2021)

The Team will be formed voluntarily. After the approval of the protocol by CEIC, the GC will inform all the gynaecologists and midwives head services via e-mail of the aim of the present study. Head services, in the routine meetings will inform their particular service team. Head services, then, will send an e-mail with data (name, e-mail, phone number and working centre) to the GC of participating doctors and midwives.

As the standardization of the data collection is very important, the GC will send the protocol via e-mail to the enrolled team (those who will take part in the study). The whole research team will keep in contact via e-mail and/or by way of telephone.

After the above has taken place, three meetings will be held by the GC which will take place in the HTVC which will be attended by the main investigators, the gynaecologists and the midwives who will be enrolled in the project.

- First meeting: presentation of the study design, establishment of the steps of the study with the chronogram and definition of the role of each of the members of the team. With the objective to standardize the process and there will be also a focus on the questionnaire and scores collection methods.

- Second meeting: recap on previous issues and help with any clarification and doubts before the participants recruitment.

- Third meeting: will take place with the data collection process ending in order to facilitate it to the GC, and so, they can start working with the SA.

12.2.4 STAGE 3: Participants Recruitment (December 2021 – April 2024)

The recruitment will be done by gynaecologists and midwives from the different medical centres belonging to ICS in Terres de l'Ebre region. The sample will be formed by patients who attend these centres for their follow-up visits and meet inclusion and exclusion criteria. They will be informed of the clinical, legal and ethical aspects of the study and will be given the information sheet (Annex 6). If they are interested in participating in the study, they will be asked to sign the informed consent (Annex 7).

We estimate 28,2 months (we have approximated to 29 months in the chronogram) to complete the recruitment. However, if the amount in this period is not sufficient, the time of recruitment will increase.

12.2.5 STAGE 4: Data Collection and Sample Analysis (December 2021 – July 2024)

This period will start simultaneously with the recruitment of patients but will end 3 months after the last participant is included in the study in order to process the latest data.

After having signed the informed consent, the participants will be given the questionnaire (Annex 9) and scores sheets (Annex 10 and Annex 11) in order to answer them. This will take place in an office in the same centre the patient has visited.

Available information from the medical history will be collected from SAP and ECAP programmes.

In this way, the midwife or gynaecologist who has done the exploration will be given the CSS score sheet (Annex 12) in order to fill it in.

If the information related to BMI and extra-genital affection is not available in the medical record, a physical examination will need to be assessed by a doctor or a nurse.

12.2.6 STAGE 5: Data Analysis (April 2024 – September 2024)

A common database will be created by the SA in order to register personal and medical information about the patients.

12.2.7 STAGE 6: Results Interpretation and Writing (October 2024 – December 2024)

At the end of the process of patient recruitment and data collection, the SA and main investigators will analyse the data collected. The results will be interpreted, and conclusions will be extracted. After that, the final results and conclusions will be written in the final article.

The results will be obtained by univariate analysis by a statistician. A qualified statistician will process the data collected performing a descriptive analysis.

12.2.8 STAGE 7: Dissertation, Publication and Dissemination (January 2025 – March 2025)

The GC will write up an article including the results, discussion and conclusions of the study.

Once the report is written, it will be published as an article and presented to national congresses from *Sociedad Española de Ginecología y Obsterícia* (SEGO) and AEPCC and to the journal "Progresos" from SEGO.

12.3 CHRONOGRAM

WORK PLAN	DESCRIPTION	RESPONSIBLE PERSONNEL	2021				2022				2023				2024				2025			
			Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
STAGE 0	Protocol design and protocol development	Main investigators																				
STAGE 1	Acceptance	Main investigators and Ethics Committee																				
STAGE 2	Coordination and organization	Main investigators																				
STAGE 3	Participants recruitment	Gyneacologyst and midwives enorlled and GC																				
STAGE 4	Data collection and sample analysis	Gyneacologyst and midwives enorlled, GC and SA																				
STAGE 5	Data analysis	SA																				
STAGE 6	Results interpretation and writing	Main investigators and SA																				
STAGE 7	Dissertation, publication and dissemination	Main investigators																				

13 BUDGET

The budget encompasses all the possible expenses that will be needed to accomplish this study. The research team will be formed by gynaecologists and midwives who will perform the explorations and CSS score collection. Most of the procedures are already performed in the centres included in the study and most of the required staff already work in them, so the exploration is included in their daily duties. These tasks (explorations and CSS score collection) are counted as zero expenses.

1. **Material expenses**:
   1.1. Each patient will receive 1 information sheet (3 sides), 1 informed consent (2 sides), 1 questionnaire (6 sides), 1 FGSIS score (1 side) and 1 DLQI score (2 sides). The GC will receive 1 questionnaire (3 sides) and the clinician will receive 1 CSS score (1 side). We will order 282+30 copies of each document.
2. **Personnel expenses**
   2.1. We will require the hiring of a Statistics specialist in order to code patients, carry out data quality control and statistical analysis. We estimate that they will be needed mainly during the period from the end of the data collection to the conclusion of the study (8 months). The estimated salary will be 35€ per hour and approximately 80 hours of statistical support will be needed. Then, the estimated cost will be 2800€.
   2.2. An external General coordinator will be hired to ensure the correct development of the project. This figure is indispensable due to the multi-centric character of the study.
3. **Publication and dissemination expenses**: we include the cost of the article publication in the journal "Progresos" of SEGO and the attendance at the national congresses of SEGO and AEPCC.
4. **Personal costs and services**
   4.1. **Travel expenses and allowances:** as the study is multi-centric, we will arrange three meetings before starting the data collection in Tortosa. They will take place in the HTVC so the meeting room will be for free. We will need transport and meals for all the participating investigators. The estimated money for the transport is 0,19 cts/kilometre and 15€ per meal per person. In total, there are 9 gynaecologists and 12 midwives in the region of Terres de l'Ebre.
   4.2. **Special training:** we do not know if a seminar in order to form all the medical personnel in exploring VLS will be necessary, but we will consider it for the budget. It will take place in the HTVC so the meeting room will be for free. We will need transport and

meals for all the participating investigators. The estimated money for the transport is 0,19 cts/kilometre and 15€ per meal per person.

ITEM	COST PER UNIT	NUMBER OF UNITS	SUBTOTAL COSTS
MATERIAL AND SERVICES			**280,8 €**
Document printing	*0,05€ / side*	*18 sides, 312copies*	*280,8 €*
PERSONNEL EXPENSES			**50.400 €**
Statistical specialist	*30€/hour*	*X 80 hours*	*2.400€*
General coordinator	*12.000€/year (part time)*	*4 years*	*48.000€*
PUBLICATION AND DISSEMINATION EXPENSES			**3.200€**
Article publication	*2000€*		*2000€*
Congresses	*600€*	*x2*	*1.200€*
PERSONNEL COSTS AND SERVICES			**2.217,6€**
Travel exp. & allowances	*0,19€ / km*	*60 km x 21 healthcare personnel x 3 meetings*	*718,2€*
	15€/meal	*x 21 healthcare personnel x 3 meetings*	*945€*
Special training	*0,19€ / km*	*60 km x 21 healthcare personnel*	*239,4€*
	15€/meal	*x 21 healthcare personnel*	*315€*
		TOTAL COST	**56.098,4 €**

14 CLINICAL AND HEALTHCARE IMPACT

Vulvar lichen sclerosus (VLS) is a very impairing disease in many fields and with a lot of impact in women's lives who are suffering from it. It leads, amongst others, to soreness, itching, irritation, dyspareunia, urinary complications, vulva cancer as well as affecting the psychologic and sexual sphere. So, VLS is a condition that culminates in an impaired quality of life.

There is no cure, as we see in our daily clinical practice and as studies also confirms it. VLS requires a very close treatment with a long follow-up and the number of relapses are high.

For this reason, we are proposing this study. Our main goal is to know more about the different conditions of our patients so that we can provide personal care in the different spheres and a more effective treatment in the near future.

If the results obtained in this study are relevant and our hypothesis of a possible risk factor that is still unknown is accomplished, we would like to suggest a further project in order to evaluate it in more detail.

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16 ANNEXES

16.1 **ANNEX 1**: 2006 ISSVD Classification of Vulvar Dermatoses: Pathologic Subsets and their Clinical Correlates adapted from (1)

Spongiotic pattern	Atopic dermatitis
	Allergic contact dermatitis
	Irritant contact dermatitis
Acanthotic pattern (formerly squamous cell hyperplasia)	Psoriasis
	Lichen simplex chronicus - Primary (idiopathic) - Secondary (superimposed on lichen sclerosus, lichen planus or other vulvar disease)
Lichenoid pattern	Lichen sclerosus
	Lichen planus
Dermal homogenization/sclerosus pattern	Lichen sclerosus
Vesiculobullous pattern	Pemphigoid, cicatricial type
	Linear IgA disease
Acantholytic pattern	Hailey-Hailey disease
	Darier's disease
	Papular genitocrural acantholysis
Granulomatous pattern	Crohn's disease
	Melkersson-Rosenthal syndrome
Vasculopathic pattern	Aphthous ulcers
	Behçet's disease
	Plasma cell vulvitis

Figure 1. 2006 ISSVD Classification of Vulvar Dermatoses: Pathologic Subsets and their Clinical Correlates adapted from (1)

16.2 **ANNEX 2**: 2011 ISSVD Clinical Classification of Vulvar Dermatological Disorders adapted from (2)

Table 1. 2011 ISSVD Clinical Classification of Vulvar Dermatological Disorders adapted from (2)

1) Skin-colored lesions
    A. Skin-colored papules and nodules
        1. Papillomatossi of the vestibule and medial labia minora (a normal finding; not a disease)
        2. Molluscum contagiosum
        3. Warts (HPV infection)
        4. Scar
        5. Vulvar intraepithelial neoplasia
        6. Skin tag (acrochordon, fibroepithelial polyp)
        7. Nevus (intradermal type)
        8. Mucinous cyst of the vestibule and medial labia minora (may have yellow hue)
        9. Epidermal cyst (syn. epidermoid cyst; epithelial cyst)
        10. Mammary-like gland tumor (hidroadenoma papilliferum)
        11. Bartholini gland cyst and tumor
        12. Syringoma
        13. Basal cell carcinoma
    B. Skin-colored plaques
        1. Lichen simplex chronicus and other lichenified disease (see definitions in Discussion of Terms Related to Eczematous and Lichenified Diseases)
        2. Vulvar intraepithelial neoplasia
2) Red lesions: patches and plaques
    A. Eczematous and lichenified diseases (see definitions in Discussion of Terms Related to Eczematous and Lichenified Diseases)
        1. Allergic contact dermatitis
        2. Irritant contact dermatitis
        3. Atopic dermatitis (rarely seen as a vulvar presentation)
        4. Eczematous changes superimposed on other vulvar disorders
        5. Diseases clinically mimicking eczematous disease (candidiasis, Hailey-Hailey disease, and extramammary Paget disease)

6. Lichen simplex chronicus (lichenification with no preceding skin lesions)
7. Lichenification superimposed on an underlying preceding pruritic disease

B. Red patches and plaques (no epithelial disruption)

1. Candidiasis
2. Psoriasis
3. Vulvar intraepithelial neoplasia
4. Lichen planus (LP)
5. Plasma cell (Zoon) vulvitis
6. Bacterial soft-tissue infection (cellulitis and early necrotizing fasciitis)
7. Extramammary Paget disease

3) Red lesions: papules and nodules

A. Red papules

1. Folliculitis
2. Wart (HPV infection)
3. Angiokeratoma
4. M. contagiosum (inflamed)
5. Hidradenitis suppurativa (early lesions)
6. Hailey-Hailey disease

B. Red nodules

1. Furuncles (''boils'')
2. Wart (HPV infection)
3. Prurigo nodularis
4. Vulvar intraepithelial neoplasia
5. M. contagiosum (inflamed)
6. Urethral caruncle and prolapse
7. Hidradenitis suppurativa
8. Mammary-like gland adenoma (hidradenoma papilliferum) 9. Inflamed epidermal cyst
9. Bartholin duct abscess
10. Squamous cell carcinoma
11. Melanoma (amelanotic type)

4) White lesions

A. White papules and nodules

1. Fordyce spots (a normal finding; may sometimes have a yellow hue)
2. M. contagiosum
3. Wart
4. Scar
5. Vulvar intraepithelial neoplasia
6. Squamous cell carcinoma
7. Milium (pl. milia)
8. Epidermal cyst
9. Hailey-Hailey disease

B. White patches and plaques

1. Vitiligo
2. Lichen sclerosus
3. Post-inflammatory hypopigmentation
4. Lichenified diseases (when the surface is moist→see definitions in Discussion of Terms Related to Eczematous and Lichenified Diseases)
5. Lichen planus (LP)
6. Vulvar intraepithelial neoplasia
7. Squamous cell carcinoma

5) Dark-colored (brown, blue, gray, or black) lesions

A. Dark colored patches

1. . Melanocytic nevus
2. Vulvar melanosis (vulvar lentiginosis)
3. Post-inflammatory hyperpigmentation
4. Lichen planus (LP)
5. Acanthosiaas nigricans
6. Melanoma in situ

B. Dark-colored papules and nodules

1. Melanocytic nevus (includes those with clinical and/or histological atypia)
2. Warts (HPV infection)
3. Vulvar intraepithelial neoplasia
4. Seborrheic keratosis
5. Angiokeratoma (capillary angioma, cherry angioma)
6. Mammary-like gland adenoma (hidradenoma papilliferum)
7. Melanoma

6) Blisters
    A. Vesicules and bullae
        1. Herpesvirus infections (herpes simplex, herpes zoster)
        2. Acute eczema (see definitions in Discussion of Terms Related to Eczematous and Lichenified Diseases)
        3. Bullous lichen sclerosus
        4. Lymphangioma circumscriptum (lymphangiectasia)
        5. Immune blistering disorders (cicatricial pemphigoid, fixed drug eruption, Steven-Johnson syndrome, pemphigus)
    B. Pustules
        1. Candidiasis (candidiosis)
        2. Folliculitus
7) Erosions and ulcers
    A. Erosions
        1. Excoriations (see the disorders in group 2A)
        2. Erosive lichen planus
        3. Fissures arising on normal tissue (idiopathic, intercourse related)
        4. Fissures arising on abnormal tissue (candidiasis, lichen simplex chronicus, psoriasis, Crohn disease, etc.)
        5. Vulvar intraepithelial neoplasia, eroded variant
        6. Ruptured vesicles, bullae and pustules (see all of the disorders listed in group 6 ''blisters'')
        7. Extramammary Paget disease
    B. Ulcers
        1. Excoriations (related to eczema, lichen simplex chronicus) 2. Aphthous ulcers (syn. aphthous minor), aphthous major,
        2. Lipschu¨ tz ulcer (occurring either as an idiopathic process or secondary to other diseases such as Crohn, Behc¸et, various viral infections)
        3. Crohn disease
        4. Herpesvirus infection (particularly in patients who are immunosuppressed)
        5. Ulcerated squamous cell carcinoma
        6. Primary syphilis (chancre)
8) Edema (diffuse genital swelling)

A. Skin-colored edema
    1. Crohn disease
    2. Idiopathic lymphatic abnormality (congenital Milroy disease)
    3. Postradiation and postsurgical lymphatic obstruction
    4. Postinfectious edema (especially staphylococcal and streptococcal cellulitis)
    5. Postinflammatory edema (especially hidradenitis suppurativa)
B. Pink or edema
    1. Venous obstruction (e.g., pregnancy and parturition)
    2. Cellulitis (primary or superimposed on already existing edema)
    3. Inflamed Bartholin duct cyst/abscess
    4. Crohn disease
    5. Mild vulvar edema may occur with any inflammatory vulvar disease

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ISSVD indicates International Society for the Study of Vulvovaginal Disease; HPV, human papillomavirus.

16.3 **ANNEX 3**: Diagnose of Vulvar Lesions According to 2011 ISSVD Terminology and Classification of Vulvar Dermatological Disorders (2)

- **Step 1**. Define the lesion by choosing 1 or more of the following nouns: blister, bulla, cyst, oedema, erosion, excoriation, fissure, lesion, macule, nodule, papule, patch, plaque, pustule, rash, ulcer and vesicle.
- **Step 2**. Choose appropriate adjectives to modify the noun(s) chosen previously: colour, surface, margination, configuration.
- **Step 3**. Formulate a list of differential diagnosis. Using steps 1 and 2, we can place the vulvar disease into 1 of the 8 disease groups (Annex 2).
- **Step 4**. Reduce the number of diagnoses in the list of differential diagnosis. With the help of a textbook and patient's history, it is normally sufficient to determine the most likely diagnoses or, at the very least, reduce the list to 2 or 3 possibilities.
- **Step 5**. Confirm a clinical diagnosis. In some cases, we will need a biopsy for histological confirmation. It is possible that the pathologist may not be able to offer a single best diagnosis but, instead, a pattern. In this situation, correlation between clinical features and histological patterns should be run.

16.4 **ANNEX 4**: Comparison of Common Vulvar Dermatoses adapted from (32)

Table 2. Comparison of Common Vulvar Dermatoses adapted from (32)

	Contact Dermatitis	**Lichen Simplex Chronicus**	**Lichen Sclerosus**	**Lichen Planus**	**Psoriasis**
Presentation	Affects all ages; acute or chronic itching or burning	Primarily mid- to late adult life, although can affect all ages; chronic itching ("itch-scratch-itch"	Prepubescent girls and post-menopausal women; chronic itching irritation, dyspareunia	Primarily affects peri-menopausal and menopausal women; erosive mucocutaneous—chronic burning, dyspareunia	Can begin at any age; peak onset 30s and 50-70 y; chronic itching; often misdiagnosed as cutaneous candidiasis or tinea
Lesion characteristics	Poorly demarcated, various degrees of erythema	Various degrees of erythema, scaling and lichenified plaques, may have some excoriation from the scratches.	"Tissue paper" skin, thinned, whitened and crinkling plaques. Köbner phenomenon, scarring dermatosis; loss of vulvar architecture.	Well-demarcated erosions; Wickham's striae are pathopneumonic, scarring dermatosis, loss of vulvovaginal architecture (may affect mouth and vagina)	Well-demarcated pink plaques; scale typical of extragenital psoriasis often not seen with genital involvement as a result of moisture, Köbner phenomenon
Biopsy	Biopsy if diagnosis uncertain	Biopsy if diagnosis uncertain	Consider biopsy to confirm diagnosis	Consider biopsy to confirm diagnosis	Consider biopsy to confirm diagnosis

16.5 **ANNEX 5**: Treatment Algorithm of LS adapted from (12)

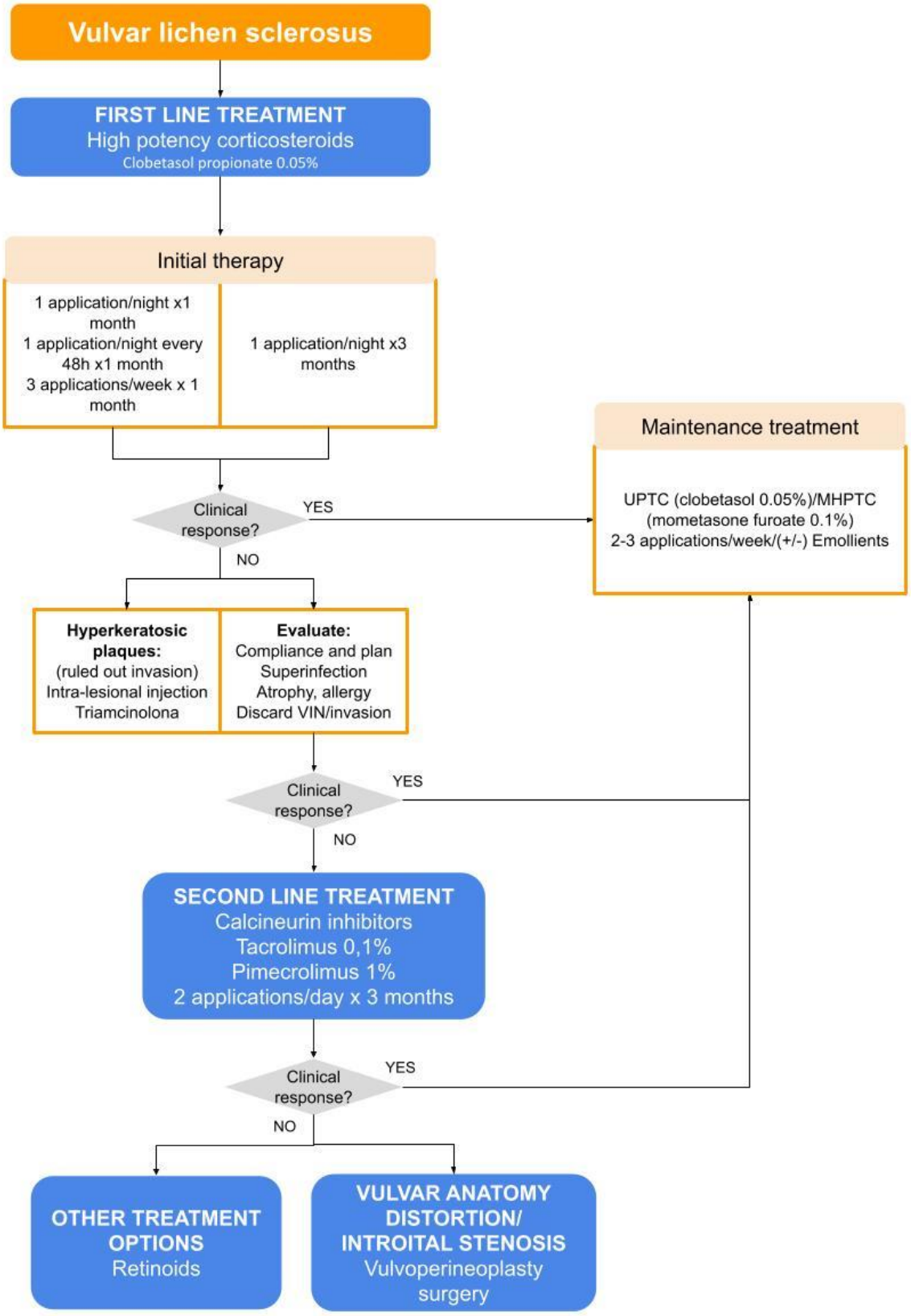

Figure 12. Treatment Algorithm of LS adapted from (12)

16.6 **ANNEX 6**: Information Sheet

FULL D'INFORMACIÓ PER A LA PARTICIPANT DE L'ESTUDI

DADES DE L'ESTUDI

Títol de l'estudi: perfil clínic i demogràfic de la dona diagnosticada de liquen esclerós vulvar a la regió de les Terres de l'Ebre.

Investigadores principals: Dra. Lara Colomé Ceballos, Servei de Ginecologia i Obstetrícia, Hospital de Tortosa Verge de la Cinta i Cinta Ferrando Piñana, estudiant de Grau en Medicina a la Facultat de Medicina de la Universitat de Girona.

Centres que participen en l'estudi:

- Baix Ebre: ABS Ametlla - Perelló, ABS Tortosa -Est, ABS Tortosa -Oest, ABS Aldea - Camarles - Ampolla, ABS Deltebre, ASSIR CAP Baix Ebre, Hospital Verge de la Cinta de Tortosa.

- Montsià: ABS Ulldecona - La Sènia, ABS Amposta, ABS Sant Carles - Alcanar.

- Terra Alta: ABS Terra Alta.

- Ribera d'Ebre: ABS Flix, ABS Móra La Nova - Móra d'Ebre.

Aquest document té per objecte informar-la sobre un projecte d'investigació en el qual se la convida a participar. Aquest projecte ha estat aprovat pel Comitè Ètic d'Investigació Clínica de l'Hospital de Tortosa Verge de la Cinta. L'objectiu d'aquest full d'informació és que rebi la informació correcta i suficient per a que pugui avaluar, jutjar i decidir si vol o no participar en aquest projecte. Per a això, llegeixi aquest full informatiu amb atenció i nosaltres li aclarirem els dubtes que li puguin sorgir. A més, pot consultar amb les persones que consideri oportú.

Aquest estudi forma part del projecte de recerca de Fi de Grau de l'estudiant de Medicina Cinta Ferrando Piñana i està tutoritzat per la Dra. Lara Colomé Ceballos, ginecòloga i obstetra de l'Hospital de Tortosa Verge de la Cinta.

PARTICIPACIÓ

Se la convida a participar en un estudi observacional en el qual es pretén estudiar el perfil clínic i sociodemogràfic de les dones amb diagnòstic de liquen esclerós vulvar.

Ha de saber que la seva participació en aquest estudi és totalment voluntària i que pot decidir no participar o abandonar l'estudi i així retirar el consentiment en qualsevol moment, sense la necessitat de cap justificació i sense que això alteri la relació amb el seu metge o la seva metgessa ni que es produeixi cap perjudici en el seu tractament.

Participar en l'estudi implica accedir a la seva informació clínica disponible al programa "SAP" o al programa "ECAP" utilitzats en la pràctica clínica diària, respondre un qüestionari bàsic que inclou preguntes sobre el seu estat civil, nivell d'educació, els seus hàbits tòxics, aspectes de la seva malaltia i la seva vida sexual així com emplenar dues escales que avaluen la seva salut sexual i la seva qualitat de vida referides amb el seu diagnòstic. Altrament, el seu metge o metgessa o la llevadora que l'explori aportarà informació sobre l'estat de la seva malaltia a través de l'emplenament d'una escala que avalua la severitat de la seva malaltia.

La participació per part del coordinador general (investigador principal) i de l'estadístic serà compensada econòmicament. Altrament, la seva participació en l'estudi com a pacient és totalment gratuïta i no s'obtindrà cap compensació econòmica.

ÚS DE LES SEVES DADES

Per al present estudi la seva informació personal com a part del projecte serà utilitzada únicament per a la realització del mateix. S'adoptaran les mesures per a garantir la confidencialitat de les seves dades, així doncs la seva privacitat estarà protegida i regulada per la *"Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales"* i les dades recollides seran gestionades de forma anònima i només utilitzades amb fins d'investigació.

Les conclusions de la investigació serviran per a beneficiar tant a la participant com a altres persones, i aquestes seran adequadament utilitzades per a assolir els objectius de l'estudi i serviran de base per a futures investigacions en aquest àmbit.

INFORMACIÓ DELS RESULTATS D'INVESTIGACIÓ

La participant està en el seu dret de ser informada dels resultats de la investigació. En el cas que aquestes investigacions proporcionin dades que puguin ser clínica o genèticament rellevants per a vostè i interessar per a la seva salut o la de la seva família, li seran comunicades si així ho estima oportú. Si vostè no desitja rebre aquesta informació, tingui en compte que la llei estableix que, quan la informació obtinguda sigui necessària per evitar un greu perjudici per a la salut dels seus familiars biològics, un comitè d'experts estudiarà el cas i haurà de decidir si és convenient informar als afectats o als seus representants legals.

Si per alguna raó vostè volgués conèixer els resultats de les investigacions que s'hagin produït com a conseqüència de la seva col·laboració, podrà posar-se en contacte amb els responsables

del projecte, que la informaran degudament. Pot contactar amb l'alumna Cinta Ferrando Piñana a través del seu correu electrònic (cintaferrando96@gmail.com).

MOLÈSTIES

És possible que de la seva participació en aquest estudi no obtingui un benefici directe. No obstant això, l'avaluació del perfil prèviament explicat podria contribuir a millorar el pronòstic i tractament en futures pacients.

Recordi que la seva participació en l'estudi és totalment voluntària i, si decideix no participar rebrà tota l'atenció mèdica que necessiti i la relació amb l'equip mèdic que l'atén no es veurà afectada.

Moltes gràcies per la seva col·laboració.

16.7 **ANNEX 7:** Informed Consent

FORMULARI DE CONSENIMENT INFORMAT A LA PACIENT DE L'ESTUDI

Títol de l'estudi: perfil clínic i demogràfic de la dona diagnosticada de liquen esclerós vulvar a la regió de les Terres de l'Ebre.

Jo (nom i cognoms), _____, amb DNI _____:

- He llegit i entès la fulla informativa sobre l'estudi que se m'ha entregat.
- He pogut fer preguntes sobre l'estudi i els meus dubtes han quedat resolts satisfactòriament.
- He parlat amb les investigadores principals, o algun dels seus col·laboradors en l'estudi.
- He rebut suficient informació sobre l'estudi.
- He estat informada de les implicacions i finalitats de l'estudi.
- Comprenc que la meva participació és voluntària.
- Comprenc que puc retirar-me de l'estudi en qualsevol moment, sense donar explicacions i sense que aquest fet comporti repercussions en la meva assistència mèdica i els meus drets.
- Comprenc que les meves dades seran tractades de manera confidencial i utilitzades exclusivament per finalitats científiques en relació a l'estudi

Així doncs, dono voluntàriament el meu consentiment per a participar en aquest estudi així com per al tractament de les meves dades personals i de salut que l'estudi requereixi.

Firma de la participant:

Data: __ /__ /__
Lloc: _____

Firma de l'investigador principal:

Data: __ /__ /__
Lloc: _____

Hospital de Tortosa Verge de la Cinta (HTVC)

*Tant el Full d'Informació a la pacient com el Consentiment Informat estaran disponibles en una versió catalana i una castellana, adaptant-se així a les preferències de la pacient.

Aquest document es firmarà per duplicat quedant-se una còpia l'investigador i una altra la pacient

REVOCACIÓ DEL CONSENTIMENT

Jo (nom i cognoms)_____ amb DNI _____ revoco el consentiment prèviament firmat par a la participació en l'estudi a sobre indicat.

Firma de la participant:

Data: __ /__ /__
Lloc: _____

Firma l'investigador principal:

Data: __ /__ /__
Lloc: _____

Hospital de Tortosa Verge de la Cinta (HTVC)

*Tant el Full d'Informació a la pacient com el Consentiment Informat estaran disponibles en una versió catalana i una castellana, adaptant-se així a les preferències de la pacient.

Aquest document es firmarà per duplicat quedant-se una còpia l'investigador i una altra la pacient

16.8 **ANNEX 8:** Number of women >18 years old in the region of Terres de l'Ebre adapted from (51)

ABS	Location	Women > 18 years old	Total ABS
ABS FLIX	Riba-roja d'Ebre	469	4.459
	Flix	1.502	
	Margalef	36	
	Falset	1.172	
	La Torre de l'Espanyol	251	
	La Palma d'Ebre	156	
	Vinebre	174	
	Ascó	699	
ABS MÓRA LA NOVA-MÓRA D'EBRE	Garcia	215	5.945
	Móra la Nova	1.289	
	Móra d'Ebre	2.371	
	Benissanet	435	
	Miravet	275	
	Ginestar	315	
	Rasquera	344	
	Tivissa	701	
ABS TERRA ALTA	La Pobla de Massaluca	123	4.827
	La Fatarella	417	
	Corbera d'Ebre	421	
	El Pinell de Brai	430	
	Prat de Comte	76	
	Arnes	207	
	Horta de Sant Joan	476	
	Bot	249	
	Gandesa	1.246	
	Caseres	114	
	Batea	799	
	Vilalba dels Arcs	269	
ABS TORTOSA 1- EST	Tortosa	13.890	14.271
	Tivenys	381	
ABS TORTOSA 2-OEST	Benifallet	350	5.044
	Paüls	244	
	Xerta	525	
	Aldover	389	
	Alfara de Carles	150	
	Roquetes	3.131	
	Mas de Barberans	255	
ABS AMETLLA-PERELLÓ	El Perelló	1.121	3.959
	L'Ametlla de Mar	2.838	

ABS ALDEA-CAMARLES-AMPOLLA	L'Ampolla	1.356	4.326
	Camarles	1.338	
	L'Aldea	1.632	
ABS DELTEBRE	Deltebre	4.776	6.214
	Sant Jaume d'Enveja	1.438	
ABS AMPOSTA	Freginals	158	11.076
	Godall	250	
	La Galera	307	
	Santa Bàrbara	1.508	
	Masdenverge	444	
	Amposta	8.409	
ABS ULLDECONA-LA SÈNIA	La Sènia	2.365	4.855
	Ulldecona	2.490	
ABS SANT CARLES-ALCANAR	Sant Carles de la Ràpita	6.328	10.245
	Alcanar	3.917	
		TOTAL	**75.221**

16.9 ANNEX 9: Sociodemographic and Clinical Data Collection

QÜESTIONARI A EMPLENAR PER LA PACIENT

ESTUDI: perfil clínic i demogràfic de la dona diagnosticada de liquen esclerós vulvar a les Terres de l'Ebre.

Li agraïm molt que contesti aquest qüestionari, ja que serà de gran utilitat per a la realització del nostre estudi. La seva informació serà tractada de manera absolutament confidencial.

Si us plau, **marqui només una casella per pregunta i ompli els espais en buit si així ho precisa la pregunta**. No dubti en preguntar si té algun dubte.

Número d'identificació (codi):

Data de naixement (dd/mm/aaaa):

E-mail:

Telèfon:

Data (dd/mm/aaaa):

Centre assistencial:

Sanitari/sanitària al càrrec de la pacient:

DADES PERSONALS

Edat de la pacient: ____

DADES SOCIODEMOGRÀFIQUES

Nivell d'estudis (marqui el nivell més alt d'estudis assumit):

☐ No estudis o estudis de primària ☐ Estudis de secundària ☐Grau universitari

Ocupació:

☐ Gestora/professional universitària/directora

☐ Autònoma/ocupació intermèdia (ocupació que no apareix nombrada a les opcions)

☐ Treballadora manual

Situació laboral: ☐Treballadora activa ☐Treballadora de la llar ☐Aturada

Estat civil:

☐ Soltera
☐ Casada
☐ Divorciada
☐ Separada
☐ Vídua
☐ Parella estable
☐ Prefereixo no contestar

ANTECEDENTS TÒXICS

Pel que fa al **consum de tabac**, marqui una de les següents caselles:

☐ No he fumat mai

☐ Ex-fumadora (actualment no fuma o porta més d'un any sense fumar)

☐ Fumadora (almenys 1 cigarreta en l'últim any)

En cas que la resposta anterior sigui "fumadora", indiqui els **paquets/any**: ____

Ha consumit alguna de les següents **drogues** en l'últim any?

Alcohol	☐ Sí	☐ No
Cànnabis	☐ Sí	☐ No
Opiacis	☐ Sí	☐ No
Cocaïna	☐ Sí	☐ No
Amfetamines	☐ Sí	☐ No
Heroïna	☐ Sí	☐ No

En cas que alguna de les respostes anteriors sigui afirmativa, amb quina **freqüència** n'ha consumit?

Alcohol	☐ Cada dia	☐ Un cop a la setmana	☐ Un cop al mes	☐ Un cop a l'any
Cànnabis	☐ Cada dia	☐ Un cop a la setmana	☐ Un cop al mes	☐ Un cop a l'any
Opiacis	☐ Cada dia	☐ Un cop a la setmana	☐ Un cop al mes	☐ Un cop a l'any

Cocaïna ☐ Cada dia ☐ Un cop a la setmana ☐ Un cop al mes ☐ Un cop a l'any

Amfetamines ☐ Cada dia ☐ Un cop a la setmana ☐ Un cop al mes ☐ Un cop a l'any

Heroïna ☐ Cada dia ☐ Un cop a la setmana ☐ Un cop al mes ☐ Un cop a l'any

INFORMACIÓ RELACIONADA AMB EL SEU DIAGNÒSTIC DE LÍQUEN ESCLERÓS VULVAR

Quant fa que la van **diagnosticar** de liquen esclerós vulvar? Anys: _____

Ha dut a terme algun **tractament durant l'últim any**? ☐ Sí ☐ No

Quin o quins **tractaments** ha fet **durant l'últim any**?

Propionat de clobetasol 0,05% ☐ Sí ☐ No

Clarelux® (espuma cutània 500mcg/g) ☐ Sí ☐ No

Clobisdin® (solució cutània 500mcg/g) ☐ Sí ☐ No

Clovate® (Crema 0,5mg/g) ☐ Sí ☐ No

Decloban® (pomada 0,5mg/g) ☐ Sí ☐ No

Halobetasol 0,05% ☐ Sí ☐ No

Ultravate® ☐ Sí ☐ No

Furoat de mometasona 0,1% ☐ Sí ☐ No

Elica® ☐ Sí ☐ No
Elocom® ☐ Sí ☐ No
Konex® ☐ Sí ☐ No

Tacrolimus ☐ Sí ☐ No

Protopic® ☐ Sí ☐ No

Pimecrolimus ☐ Sí ☐ No

Elidel® ☐ Sí ☐ No

Rizan® ☐ Sí ☐ No

Emolients ☐ Sí ☐ No

Methylprednisolon aceponate (0,1%) ☐ Sí ☐ No

Lexxema® ☐ Sí ☐ No

Tractament excisional (cirurgia) ☐ Sí ☐ No

Ha necessitat mai algun dels següents **tractaments al llarg de la seva malaltia**?

Vulvoperineoplàstia ☐ Sí ☐ No
Retinoides tòpics ☐ Sí ☐ No
Retinoides orals ☐ Sí ☐ No

Ha hagut de **canviar de tractament** al llarg de la seva malaltia? ☐ Sí ☐ No

En cas que la resposta anterior sigui afirmativa, indiqui el **motiu** pel qual va haver o ha hagut de canviar de tractament.

Reacció adversa ☐ Sí ☐ No
Infeccions secundàries ☐ Sí ☐ No
No milloria dels símptomes tot i un correcte tractament ☐ Sí ☐ No

Quants de **mesos** ha estat **sense símptomes** des que va acabar l'últim tractament o des de que ha començat un tractament fins el dia d'avui? Mesos: ____

Quantes vegades ha hagut de **tornar a començar un tractament** al llarg de la seva malaltia després d'haver deixat el que estava fent? Número de vegades: ____

Fa algun **seguiment** de la seva malaltia almenys 1 cop a l'any des del seu diagnòstic amb algun o alguna professional de la salut? ☐ Sí ☐ No

Amb quin o quins **professionals de la salut** realitza el **seguiment** de la seva malaltia?

Metge o metgessa de família ☐ Sí ☐ No
Ginecòleg/a ☐ Sí ☐ No
Dermatòleg/a ☐ Sí ☐ No

Hi ha algun o alguna **familiar** seu que tingui o hagi tingut liquen esclerós genital? ☐ Sí ☐ No

En el cas que la resposta anterior sigui afirmativa, marqui quin **grau de parentesc** té o tenen amb vostè.

Primer grau ☐ Sí ☐ No
Segon grau ☐ Sí ☐ No
Tercer grau ☐ Sí ☐ No

INFORMACIÓ SOBRE LA SEVA HIGENE ÍNTIMA, PARITAT I VIDA SEXUAL

Duu a terme una **higiene específica de la vulva cada dia**? ☐ Sí ☐ No

Utilitza algun **sabó especial** (gel íntim) per a la higiene de la seva vulva (independentment de la resposta anterior)? ☐ Sí ☐ No

Ha **donat mai a llum?** ☐ Sí ☐ No

En cas que la resposta anterior sigui afirmativa, respongui la següent pregunta. Quants de **parts via vaginal** ha tingut?
Número: ____

En cas que la resposta anterior sigui 1 o més, respongui la següent pregunta. Ha requerit **instrumentació** en algun dels seus parts via vaginal? ☐ Sí ☐ No

En cas que la resposta a la pregunta "número de parts vaginals" sigui 1 o més, respongui la següent pregunta. Ha requerit **episiotomia** en algun dels seus parts via vaginal? ☐ Sí ☐ No

En cas que la resposta a la pregunta "ha donat mai" a llum sigui afirmativa, respongui la següent pregunta. Quants parts per **cesària** ha tingut? Número: ____

En cas que la resposta a la pregunta "ha donat mai" a llum sigui afirmativa, respongui la següent pregunta. Ha fet mai **lactància** materna? ☐ Sí ☐ No

Quin és el seu estat en relació a la **menopausa**?

Pre-menopausa o peri-menopausa	☐ Sí	☐ No
Post-menopausa	☐ Sí	☐ No

Quants anys fa que està en estat de **menopausa?** Anys: ____

Ha utilitzat algun **mètode anticonceptiu** durant l'últim any? ☐ Sí ☐ No

En cas que la resposta anterior sigui afirmativa, respongui la següent pregunta. Quin **mètode anticonceptiu** ha utilitzat?

Diafragma	☐ Sí	☐ No
Anticonceptius orals combinats	☐ Sí	☐ No
Preservatiu femení	☐ Sí	☐ No
Preservatiu masculí	☐ Sí	☐ No
Implant de contracepció	☐ Sí	☐ No
Injecció de contracepció	☐ Sí	☐ No
DIU (dispositiu intrauterí)	☐ Sí	☐ No

DIU alliberador d'hormones	☐ Sí	☐ No
Simptotèrmic	☐ Sí	☐ No
Píndola de progesterona	☐ Sí	☐ No
Anell vaginal	☐ Sí	☐ No
Esterilització femenina (lligadura de trompes)	☐ Sí	☐ No
Esterilització masculina (vasectomia)	☐ Sí	☐ No

Quina és la seva **orientació sexual**?

☐ Heterosexual
☐ Homosexual/lesbiana
☐ Bisexual
☐ En dubte o incerta
☐ Asexual
☐ Prefereixo no contestar

Quin **tipus** d'activitat sexual ha tingut durant **l'últim any**??

☐ Amb penetració vaginal
☐ Amb penetració anal
☐ Masturbació
☐ Sexe oral
☐ Cap dels anteriors
☐ Prefereixo no contestar

Quantes **parelles sexuals** ha tingut al llarg de la seva vida?

Número: ____

☐ Prefereixo no contestar

QÜESTIONARI A EMPLENAR PEL COORDINADOR GENERAL

ESTUDI: perfil clínic i demogràfic de la dona diagnosticada de liquen esclerós vulvar a les Terres de l'Ebre.

Li agraïm molt que contesti aquest qüestionari, ja que serà de gran utilitat per a la realització del nostre estudi. La seva informació serà tractada de manera absolutament confidencial.

Si us plau, **marqui només una casella per pregunta i ompli els espais en buit si així ho precisa la pregunta**. No dubti en preguntar si té algun dubte.

Número d'identificació (codi):

Data de naixement (dd/mm/aaaa):

E-mail:

Telèfon:

Data (dd/mm/aaaa):

Centre assistencial:

Sanitari/sanitària al càrrec de la pacient:

DADES SOCIODEMOGRÀFIQUES

Quina és la **raça** de la pacient?

☐ Hispana / llatina
☐ Índia americana o nativa d'Alaska
☐ Asiàtica
☐ Negra o afroamericana
☐ Hawaiana nativa o altre illenca del Pacífic
☐ Blanca
☐ Dues o més races

ANTECEDENTS MÈDICS

Al·lèrgies medicamentoses: _____

Quin és l'**índex de massa corporal** de la pacient?

☐ < 18,5 kg/m^2
☐ 18,5-24,9 kg/m^2
☐ 25-29,9 kg/m^2
☐ ≥ 30 kg/m^2

INFORMACIÓ RELACIONADA AMB EL DIAGNÒSTIC DE LÍQUEN ESCLERÓS VULVAR

La pacient pateix o ha patit alguna de les següents **dermatosis vulvars** al llarg de la seva vida?

Liquen pla	☐ Sí	☐ No
Esclerodèrmia localitzada	☐ Sí	☐ No
Morfea	☐ Sí	☐ No

La pacient pateix o ha patit alguna de les següents **displàsies o neoplàsia** al llarg de la seva malaltia?

Neoplàsia intra-epitelial vulvar	☐ Sí	☐ No
Carcinoma de cèl·lules escamoses	☐ Sí	☐ No

La pacient pateix o ha patit alguna de les següents **infeccions** al llarg de la seva vida?

Virus del papil·loma humà	☐ Sí	☐ No
Virus Ebstein-Barr	☐ Sí	☐ No
Virus herpes	☐ Sí	☐ No
Virus hepatitis C	☐ Sí	☐ No
Streptococcus	☐ Sí	☐ No
Borrelia burdogferi	☐ Sí	☐ No
Candidiasi	☐ Sí	☐ No

La pacient pateix o ha patit alguna de les següents **malalties** al llarg de la seva vida?

Tiroïditis de Hashimoto	☐ Sí	☐ No
Malaltia de Graves'	☐ Sí	☐ No
Al.lopècia areata	☐ Sí	☐ No
Vitilígen	☐ Sí	☐ No
Anèmia perniciosa	☐ Sí	☐ No
Lupus eritematós sistèmic	☐ Sí	☐ No
Diabetes mellitus	☐ Sí	☐ No
Malaltia celíaca	☐ Sí	☐ No

La pacient pateix o ha patit liquen esclerós **extra-genital** al llarg de la seva vida? ☐ Sí ☐ No

INFORMACIÓ GINECOLÒGICA

En el cas que estigui en estat de **menopausa, quina ha sigut la raó?**

Fisiològica	☐ Sí	☐ No
Química	☐ Sí	☐ No
Quirúrgica	☐ Sí	☐ No

16.10 **ANNEX 10**: Female Genital Self Image Scale (FGSIS) adapted from (53)

Escala a emplenar per la pacient

Els següents ítems es refereixen a com se sent vostè amb els seus genitals (la vulva i la vagina). La paraula *vulva* es refereix als genitals externs de la dona (les parts que vostè pot veure des de l'exterior, com el clítoris, el mont pubià i els llavis de la vagina). La paraula *vagina* es refereix a la part interna, també anomenada "canal del part" (també és la part on pot entrar el penis o on es pot inserir un tampó). Si us plau, indiqui quant d'acord està o quant en desacord està amb cada afirmació.

ESCALA DE LA PRÒPIA IMATGE GENITAL FEMENINA

Si us plau, marqui amb una "X" a la casella per a indicar quant d'acord està o quant en desacord està amb cada afirmació.

Ítems	Completament en desacord	En desacord	D'acord	Completament d'acord
Em sento positiva amb els meus genitals				
Estic satisfeta amb l'aparença dels meus genitals.				
Em sentiria còmoda deixant que una parella sexual mirés els meus genitals.				
Penso que els meus genitals fan bona olor.				
Penso que els meus genitals funcionen de la manera com es suposada que haurien de funcionar.				
Em sento còmoda deixant que un professional de la salut examini els meus genitals.				
No estic avergonyida dels meus genitals.				

Resultat:

16.11 **ANNEX 11**: Dermatology Life Quality Index (DLQI) adapted from (54)

Escala a emplenar per la pacient
QÜESTIONARI SOBRE LA QUALITAT DE VIDA- DERMATOLOGIA*

L'objectiu d'aquest qüestionari consisteix en determinar quant li han afectat els seus problemes de pell en la seva vida DURANT ELS ÚLTIMS 7 DIES. Senyali, si us plau, amb una "X" un requadre de cada pregunta.

1. Durant els últims 7 dies, ha sentit **picor**, **dolor** o **coïssor** a la pell?	Molt	☐
	Bastant	☐
	Una mica	☐
	Gens	☐
2. Durant els últims 7 dies, s'ha sentit **incòmoda** o **cohibida** degut als seus problemes de pell?	Molt	☐
	Bastant	☐
	Una mica	☐
	Gens	☐
3. Durant els últims 7 dies, li han molestat els seus problemes de pell per a fer la **compra** o ocupar-se de la **casa** (o **jardí**)?	Molt	☐
	Bastant	☐
	Una mica	☐
	Gens	☐
	Sense relació	☐
4. Durant els últims 7 dies, han influït els seus problemes de pell en l'elecció de la **roba** que porta?	Molt	☐
	Bastant	☐
	Una mica	☐
	Gens	☐
	Sense relació	☐
5. Durant els últims 7 dies, han influït els seus problemes de pell en qualsevol **activitat social** o **recreativa**?	Molt	☐
	Bastant	☐
	Una mica	☐
	Gens	☐
	Sense relació	☐
6. Durant els últims 7 dies, ha tingut dificultats per a fer **deport** degut als seus problemes de pell?	Molt	☐
	Bastant	☐
	Una mica	☐
	Gens	☐
	Sense relació	☐

7. Durant els últims 7 dies, els seus problemes de pell li han impedit totalment **treballar** o **estudiar**?	Sí	☐
	No	☐
	Sense relació	☐
Si la resposta és "No": Durant els últims 7 dies, li han molestat els seus problemes de pell a la seva **feina** o **estudis**?	Bastant	☐
	Una mica	☐
	Gens	☐
8. Durant els últims 7 dies, els seus problemes de pell li han ocasionat dificultats amb la **seva parella**, **amics íntims** o **familiars**?	Molt	☐
	Bastant	☐
	Una mica	☐
	Gens	☐
	Sense relació	☐
9. Durant els últims 7 dies, li han molestat els seus problemes de pell en la seva **vida sexual**?	Molt	☐
	Bastant	☐
	Una mica	☐
	Gens	☐
	Sense relació	☐
10. Durant els últims 7 dies, el **tractament** de la seva pell li ha ocasionat problemes, per exemple ocupant-li massa temps o embrutant el seu domicili?	Molt	☐
	Bastant	☐
	Una mica	☐
	Gens	☐
	Sense relació	☐

Comprovi, si us plau, que ha contestat CADA pregunta. Moltes gràcies

Resultat:

16.12 **ANNEX 12** Physician Administered Clinical Score (CSS) adapted from (55)

Escala clínica a emplenar pel metge, metgessa o llevadora.

Inicials de la pacient _/_ Data de naixement: _ _/_ _/_ _ _ _

Ítems	Gens (0)	Moderat (1)	Sever (2)
Erosions			
Hiperqueratosi			
Fissures			
Aglutinació			
Estenosi			
Atròfia			

Data: _ _/_ _/_ _ _ _ Firma: _ _ _ _ _ _ _ _

Resultat: