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# Efficacy of topical progesterone versus topical clobetasol propionate in patients with vulvar Lichen sclerosus – A double-blind randomized phase II pilot study

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ABSTRACT

*Background:* Lichen sclerosus (LS) is a chronic inflammatory skin disease that mostly affects the anogenital region of women and lowers patients' quality of life. Current standard treatment of LS is topical steroids.
*Objective:* To evaluate the efficacy of topical progesterone 8% ointment and compare to standard therapy with topical clobetasol propionate 0.05% in premenopausal women presenting with previously untreated early onset LS.
*Study design:* Randomized, double-blind, 2-arm, single center superiority trial in premenopausal women with histologically confirmed vulvar LS who were randomized in a 1:1 ratio to receive clobetasol propionate 0.05% ointment or progesterone 8% ointment. The primary outcome was the clinical severity LS score after 12 weeks, which consists of six clinical features assessed by the physician. Secondary outcomes were the symptom severity LS score, which consists of three symptoms rated by the patient, the Short Form SF-12 physical and mental health scores, and adverse events. Response to medication was assessed by biopsy at the end of the treatment to evaluate inflammatory parameters.
*Results:* Overall, 105 women were screened, 102 underwent vulvar biopsy and 37 received a histologically confirmed diagnosis of LS and were randomized: 17 to progesterone and 20 to clobetasol propionate. At 12 weeks, the mean clinical LS scores improved from 4.6 (SD 2.0) to 4.5 (SD 1.7) in the progesterone arm, and from 4.6 (SD 2.8) to 2.9 (SD 2.2) in the clobetasol propionate arm (difference in favor of clobetasol 1.61; 95% CI 0.44 to 2.77, p = 0.009), and the mean symptom severity LS scores improved from 4.5 (SD 3.8) to 3.1 (SD 3.0) in the progesterone arm, and from 4.7 (SD 2.8) to 1.9 (SD 1.8) in the clobetasol propionate arm (difference in favor of clobetasol 1.32; 95% CI −0.25 to 2.89, p = 0.095). LS was in complete remission in 6 out of 10 patients (60%) with available biopsy in the progesterone arm, and in 13 out of 16 patients (81.3%) in the clobetasol propionate arm (odds ratio in favor of clobetasol 0.35; 95% CI 0.06 to 2.06, p = 0.234). No drug-related serious adverse event occurred during the trial.
*Conclusions:* Topical progesterone 8% ointment is inferior to standard therapy with topical clobetasol propionate 0.05% in previously untreated premenopausal women with vulvar LS after 12 weeks treatment.

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## Introduction

Lichen sclerosus (LS) is a chronic, localized, lymphocyte-mediated inflammatory skin disease which predominantly affects the anogenital region of women [1–3]. The estimated prevalence of LS is about 1.7% in patients of gynecological private practices and it is usually diagnosed in peri- or postmenopausal women [4]. LS clusters in families, which suggests genetic predisposition [5,6]. The etiology is probably multifactorial, but individual factors have not yet been identified. Trauma, injury, and sexual abuse have been suggested as possible triggers of symptoms in genetically predisposed people, which might be due to the Koebner phenomenon [3,7]. The long delays between disease onset and appropriate diagnosis may be caused by unfamiliarity with LS, inappropriate genital skin examination, and patients' reticence and embarrassment [8]. LS lowers patient quality of life, and is associated with higher risk of squamous cell cancer (SCC) of the vulva [3], therefore, early diagnosis and treatment are important.

Current standard treatments include topical steroids like clobetasol propionate 0.05%, or, as a second line treatment, calcineurin inhibitors, but the effects of therapy on the risk of VIN or SCC are unknown [8–11]. Long-term use of very potent steroids like clobetasol propionate may have the adverse effect of secondary atrophy of the skin [12], and this may make it hard to differentiate the atrophy sites from primary signs of progressive LS. In the 1970s, Jasionowski et al. examined a small case series of patients with LS and found that topical progesterone ointment were effective and well-tolerated [13,14]. In a subsequent small randomized 4-arm trial, Bracco et al found topical clobetasol propionate 0.05% superior to topical progesterone 2%, testosterone 2% and placebo [15]. However, women in this trial had advanced disease, most were post-menopausal, with a mean age of 57 years, and the concentration of progesterone ointment was low [15]. The objective of this randomized double-blind trial was to determine whether topical progesterone 8% ointment is superior to the current standard treatment of topical clobetasol propionate 0.05% ointment in reducing the clinical severity of vulvar LS in premenopausal women.

## Materials and methods

### *Trial design*

This was a single center, randomized, double-blind, 2-arm superiority pilot trial at the outpatient clinic for dysplastic genital disease of the Department of Obstetrics and Gynecology at Inselspital, Bern University Hospital, a large tertiary care center in Switzerland. The target was to randomize 62 patients, however, recruitment was stopped prematurely because of low recruitment rates and resource limitations.

### *Patients, randomization and treatment*

Women were eligible if they had vulvar lesions suspicious for LS, premenopausal status, and proven LS by biopsy. Biopsies were evaluated by one of the investigators (HB) [16]; the accuracy of the evaluation was confirmed in a blinded random sample through an independent second reader (S. Regauer, Institute of Pathology, University of Graz, Austria). Exclusion criteria were history of vulvar surgery (except episiotomy for obstetrics), signs of infection with human papilloma virus (HPV), vulvar intraepithelial neoplasia (VIN), history of immune-suppressive therapy of the vulva, and pregnancy. The trial complied with the declaration of Helsinki and was approved by the relevant research ethics board (Cantonal Ethics Committee Bern) and by Swissmedic. All women provided written informed consent.

Women were enrolled and randomized by the treating physician using sequentially numbered drug packs of identical appearance in a 1:1 ratio to receive indistinguishable ointment containing either clobetasol propionate 0.05% or progesterone 8%. The allocation sequence was computer generated by an independent statistician of CTU Bern, stratified according to severity of disease at baseline (LS-score $\leq 5$ versus $> 5$ on a standardized scale ranging from 0 to 10 with higher scores indicating higher disease severity [17]), and blocked with randomly varying block sizes of two and four, which were not communicated to the investigators. The Institute of Pharmacy of the Inselspital Bern provided the drug packs according to the allocation sequence. As each drug pack contained four tubes of identical appearance containing each 45 g of the indistinguishable study ointment, patients and investigators were blinded to the allocated treatment. After randomization, women were instructed to administer locally approximately 2 g daily of the study preparation for 12 weeks.

### *Outcomes and Follow-up*

Women were followed up 6, 12, 18, and 24 weeks after randomization, using the physician-administered clinical LS score [17], the patient-administered symptom LS score [17], and the Short Form 12 (SF-12) health-related quality of life questionnaire. The pre-specified primary outcome was the clinical LS score at 12 weeks, which consists of six clinical features (erosions, hyperkeratosis, fissures, agglutination, stenosis, and atrophy) assessed by the physician [17]. The pre-specified secondary outcomes were the clinical LS score at 6, 18 and 24 weeks, the symptom LS score at 6, 12, 18 and 24 weeks [17], the physical component score (PCS) and the mental component score (MCS) of the SF-12 at 12 and 24 weeks, and adverse events. The symptom LS score consists of three symptoms (pruritus, burning, and soreness) that are rated by the patient. All scores were standardized to range from 0 to 10. Response to medication based on histological signs of inflammation in a second biopsy at the end of treatment was an exploratory outcome; the biopsy was not mandatory.

### *Statistical analysis*

A sample size of 31 patients per group yields 80% power to detect a difference of 2 points on the original clinical LS score [17] ranging from 0 to 12 using a two-sample means test at a two-sided alpha of 0.05, assuming a standard deviation of 2.8. The corresponding large effect size of 0.71 standard deviation units is likely to be above the minimally clinically important difference. However, this was a pilot trial designed to explore the tentative efficacy of the experimental intervention, and standard deviations and correlation between baseline and follow-up, which would inform the sample size consideration for a definite trial.

Categorical data is presented as number and percentage, continuous data as mean and standard deviation. The primary analysis was by intention-to-treat, analyzing all patients in the group to which they were originally allocated, regardless of which treatment they received. Continuous outcomes were analyzed using linear regression adjusted for the outcome's baseline values. The normality of residuals was inspected by QQ-plots. To account for missing values, we used multiple imputation. The multiple imputation model included patient age at inclusion, patient age at the time of menarche, number of pregnancies, number of births, BMI, duration of complaints (all used as continuous variables), and contraception (used as categorical). We generated twenty imputed data sets, which were combined using Rubin's rules [18]. Histological remission was analyzed using a logistic regression model based on cases with complete data. Pre-specified sensitivity analyses for the clinical and the symptom LS scores included a per-protocol analysis excluding patients that did not start treatment ($n = 2$) and patients that were treated for less than 6 weeks ($n = 2$) using multiple imputation as well as a complete case analysis without multiple imputation. Post-hoc subgroup analyses for the clinical and symptom LS scores were done according to age ($\leq$35 years vs. $>$ 35 years), BMI ($\leq$25 vs. $>$ 25), duration of complaints ($\leq$1 year vs. $>$ 1 year), symptom severity, clinical severity, and sexual activity. Cutoffs used to define subgroups for symptom and clinical severity were $\leq 5$ vs $> 5$ on the respective standardized LS scores. Post-hoc analyses were planned before data lock and before any

inspection of outcome data. A statistician of an academic clinical trials unit (CTU Bern, University of Bern, Switzerland) performed all analyses in Stata, release 14 (Stata Inc, College Station, TX). The statistician was blinded when performing primary analyses.

## Results

Overall, 105 women were screened and 102 gave written informed consent and received a biopsy. Thereof, 65 were excluded as their diagnosis was not confirmed, the remaining 37 women were randomized, 17 women to progesterone, 20 to clobetasol propionate (Fig. 1). All 17 women in the progesterone arm and 18 women in the clobetasol propionate arm received treatment as allocated, whereas two women withdrew in the clobetasol group before starting treatment. Fourteen and 16 patients attended the 12 weeks assessment, respectively (Fig. 1). Randomized groups were similar in baseline characteristics, including age, BMI, oral contraceptives, number of pregnancies and births, physician-administered clinical LS score and the patient-administered

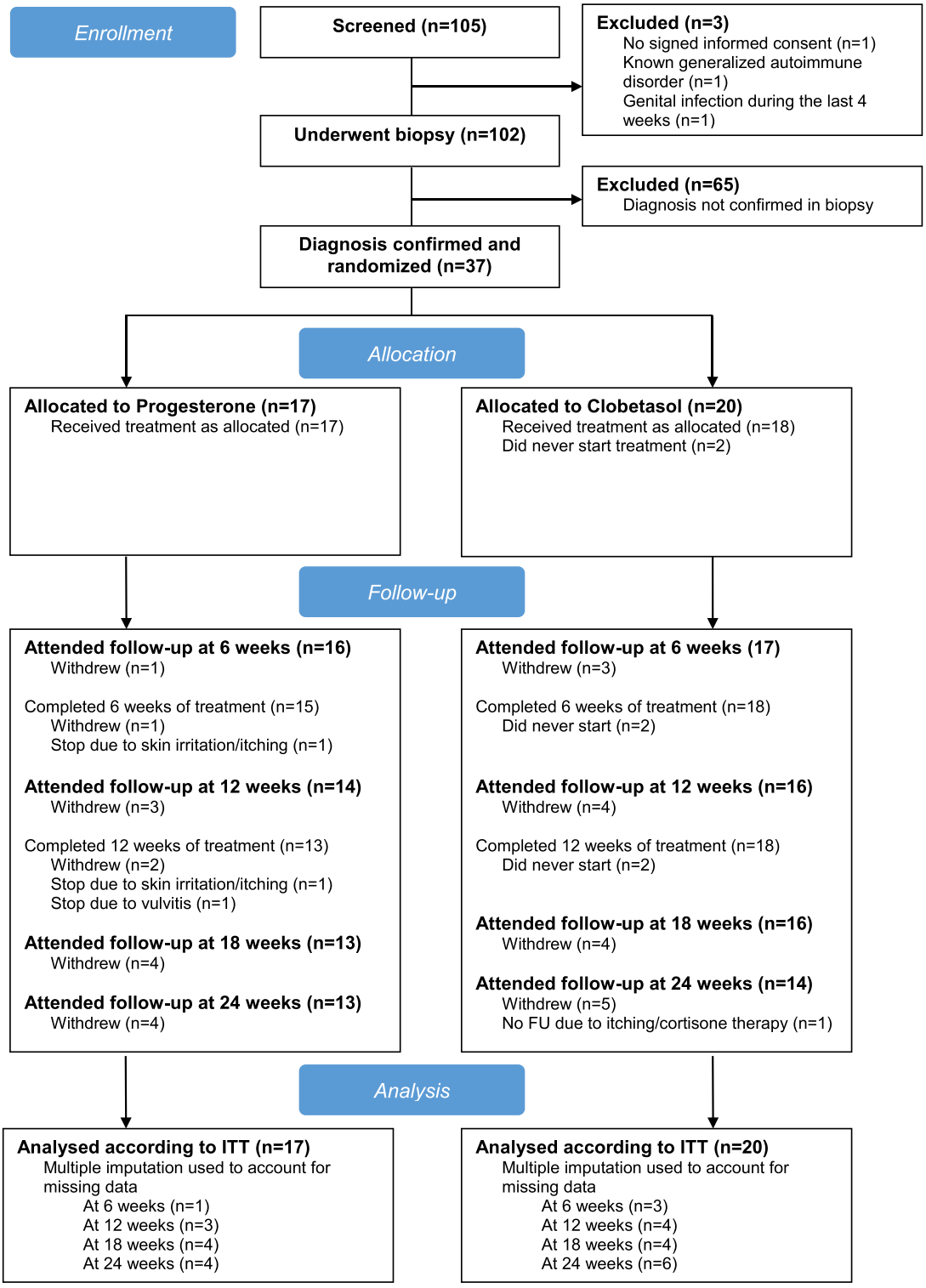


**Fig. 1.** Patient flow of enrolled patients.

symptom LS score (Table 1).

*Prespecified efficacy outcomes*

The women in the progesterone arm experienced a smaller decrease in the standardized clinical LS score at 12 weeks than the clobetasol propionate arm (mean, 4.5 vs 2.9, respectively, difference in favor of clobetasol 1.61; 95% CI 0.44 to 2.77, p = 0.009, Table 2). The progesterone arm showed a smaller decrease in the standardized symptom LS score at 12 weeks than the clobetasol propionate arm but the difference was not significant (mean, 3.1 vs 1.9, respectively, difference in favor of clobetasol 1.32; 95% CI −0.25 to 2.89, p = 0.095, Table 2). Per-protocol and complete case analyses showed similar results (supplementary Table 1). Fig. 2A and 2B present the clinical and symptom LS scores over time until 24 weeks. Post-hoc subgroup analyses for the clinical and symptom LS scores did not show any significant difference in treatment effects between subgroups (Fig. 3A – B).

The physical component of SF-12 scores numerically favored the clobetasol propionate arm at 12 weeks (mean, 5.5 vs 5.3 for clobetasol vs progesterone, respectively) and at 24 weeks (mean, 5.5 vs 5.2, respectively), but differences were not significant (Table 2). The mental component of SF-12 scores showed no difference between the two treatment arms at 12 weeks (mean, 4.4 for both groups) and at 24 weeks (mean, 4.8 vs 4.9 for clobetasol vs progesterone, respectively, Table 2). A total of 26 patients were biopsied both during screening, and at end of treatment. LS was in complete remission in six out of ten patients (60%) in the progesterone arm, and in 13 out of 16 patients (81.3%) in the clobetasol propionate arm (odds ratio 0.35, 95% CI 0.06 to 2.06, p = 0.234).

*Adverse events*

The incidence of adverse events was similar in the progesterone and the clobetasol arm (24% and 20% of patients, respectively). The incidence of severe or life-threatening adverse events (grade ≥ 3) was 12% (2/17) in the progesterone arm and 0% in the clobetasol arm (Table 3). Two patients (12%) dropped out from the progesterone arm due to skin irritation or vulvitis. One patient in the progesterone arm experienced peritonitis and had abdominal surgery but the event was classified as unrelated to the study drug.

**Table 1**
Baseline characteristics of randomized patients (N = 37) for each intervention group.

| | Progesterone (n = 17) | Clobetasol (n = 20) |
|---|---|---|
| Age | 34.3 (10.5) | 34.7 (9.7) |
| Age > 35 years | 7 (41%) | 10 (50%) |
| BMI (kg/m$^2$) | 22.7 (5.1) | 25.6 (5.6) |
| BMI > 25 | 2 (12%) | 9 (45%) |
| Diabetes mellitus | 0 (0%) | 1 (5%) |
| On oral contraceptives | 7 (41%) | 7 (35%) |
| On hormone replacement therapy | 0 (0%) | 1 (5%) |
| Age at menarche | 13.2 (1.3) | 12.8 (1.7) |
| Number of pregnancies | | |
| 0 | 10 (59%) | 10 (50%) |
| 1 | 4 (24%) | 4 (20%) |
| ≥2 | 3 (18%) | 6 (30%) |
| Number of births | | |
| 0 | 13 (76%) | 12 (60%) |
| 1 | 1 (6%) | 2 (10%) |
| ≥2 | 3 (18%) | 6 (30%) |
| Currently sexually active | 12 (71%) | 11 (55%) |
| Duration of complaints > 1 year | 10 (59%) | 15 (75%) |
| Clinical severity LS score (0–10) * | 4.6 (2.0) | 4.6 (2.8) |
| Clinical score > 5 | 6 (35%) | 8 (40%) |
| Symptom severity LS score (0–10) * | 4.5 (3.8) | 4.7 (2.8) |
| Symptom score > 5 | 9 (53%) | 8 (40%) |
| SF-12 Physical component (PCS) score (score 0–10) ** | 5.4 (0.6) | 5.1 (0.7) |
| SF-12 Mental component (MCS) score (score 0–10) ** | 4.2 (1.5) | 4.7 (1.2) |

Data are n (%) or mean (SD). * Higher scores indicate higher disease severity. ** Higher scores indicate better quality of life.

## Discussion

*Main findings*

In this randomized double-blind superiority pilot trial in women with LS the progesterone 8% ointment was found to be inferior to clobetasol propionate 0.05% in controlling clinical signs and symptoms at 12 weeks as measured by the clinical LS score and the symptom LS score, respectively. Women who received topical progesterone 8% ointment had no improvement at 12 weeks post-randomization. Conversely, those treated with clobetasol propionate 0.05% improved in clinical and symptom severity scores at 12 weeks after randomization. Both therapies were well tolerated.

*Clinical implications*

Previous reports showed potential efficacy of topical progesterone in the treatment of LS as well as an impact of progesterone on reorganization of extracellular matrix [13,14,19]. Therefore, we decided to perform a case-series of 20 consecutive premenopausal women with early onset LS who were treated successfully with topical progesterone 8% ointment [20]. Since the study of Bracco et al. [15] evaluated an older patient population than ours that presented with more advanced disease, and applied a lower concentration of progesterone ointment, we assumed that topical progesterone 8% ointment warranted further evaluation in the first-line treatment of young women with early onset of LS. However, higher concentrations of progesterone also proved inferior to clobetasol propionate in our study. Symptoms often do not to improve during short treatment schedules in younger women with vulvar LS, perhaps because of the lower baseline burden [8,15,21].

Topical clobetasol propionate 0.05% ointment remains the standard treatment for patients with vulvar LS [11]. A recent systematic review and *meta*-analysis of seven randomized trials found evidence supporting the efficacy of clobetasol proprionate, mometasone furoate, and pimecrolimus, but not of progesterone [22]. Likewise, a network *meta*-analysis of 16 observational and randomized studies found that Clobetasol treatment ranked as the best treatment for disease remission [23].

Several studies suggested that treatment with topical calcineurin inhibitors is efficacious. However, both available drugs (tacrolimus and pimecrolimus) are inferior to topical steroids and recommended as second-line treatment options only [11]. Since our study did not contain a placebo arm, we cannot exclude any efficacy of topical progesterone treatment. Therefore, topical progesterone might be an option if topical steroids or calcineurin inhibitors are contraindicated or fail. They are a potential reserve, like UV-A1 treatment or platelet-rich plasma injections [24,25].

Diagnosing LS in premenopausal women remains challenging. Many investigators reported that LS is associated with autoimmune disorders, especially thyroid disease, but no consistent pattern has emerged [3,26,27]. Despite extensive evaluation of clinical immunological parameters, no validated biomarker screening for LS exists [28]. Efforts should be made to improve diagnosis of early onset LS, including training of physicians for clinical aspects of LS and improving histopathological criteria to confirm diagnosis at early stage.

An increased incidence of LS and its associated vulvar cancer has been reported [29]. Observational studies showed long-term symptom relief and reduction of vulvar cancer when treated with topical corticosteroids, especially in strictly compliant patients [30,31]. There is controversy about the use and dosing of corticosteroids in maintenance therapy [32,33]. Our data support the use of topical corticosteroids for

**Table 2**
Score values by intervention group over the course of treatment (at 6, 12 (end of therapy), 18, and 24 weeks after start of treatment) based on multiple imputation.

| | Mean (SD) | | Difference (95% CI) | p-value |
|---|---|---|---|---|
| | Progesterone (n = 17) | Clobetasol (n = 20) | | |
| LS Clinical severity* | | | | |
| 6 weeks | 3.9 (1.9) | 3.2 (2.1) | 0.72 (-0.26 to 1.70) | 0.14 |
| 12 weeks | 4.5 (1.7) | 2.9 (2.2) | 1.61 (0.44 to 2.77) | 0.009 |
| 18 weeks | 4.2 (1.6) | 3.0 (1.7) | 1.13 (0.12 to 2.14) | 0.030 |
| 24 weeks | 3.9 (1.6) | 2.5 (1.6) | 1.42 (0.55 to 2.30) | 0.003 |
| LS Symptom severity* | | | | |
| 6 weeks | 3.7 (3.4) | 2.7 (2.4) | 1.02 (-0.90 to 2.93) | 0.29 |
| 12 weeks | 3.1 (3.0) | 1.9 (1.8) | 1.32 (-0.25 to 2.89) | 0.095 |
| 18 weeks | 3.0 (3.1) | 1.9 (2.1) | 1.19 (-0.63 to 3.01) | 0.191 |
| 24 weeks | 2.7 (3.0) | 2.1 (2.4) | 0.66 (-1.23 to 2.55) | 0.476 |
| SF-12 Physical component score** | | | | |
| 12 weeks | 5.3 (0.7) | 5.5 (0.7) | −0.30 (-0.73 to 0.12) | 0.151 |
| 24 weeks | 5.2 (0.8) | 5.5 (0.7) | −0.4 (-1.0 to 0.2) | 0.158 |
| SF-12 Mental component score** | | | | |
| 12 weeks | 4.4 (1.3) | 4.4 (1.3) | 0.41 (-0.19 to 1.02) | 0.169 |
| 24 weeks | 4.9 (1.2) | 4.8 (1.1) | 0.41 (-0.38 to 1.20) | 0.288 |

All differences were adjusted for the respective baseline scores using linear regression. *Higher values indicate higher clinical and symptom severity on LS scores. ** Higher values indicate better quality of life on SF-12 scores.

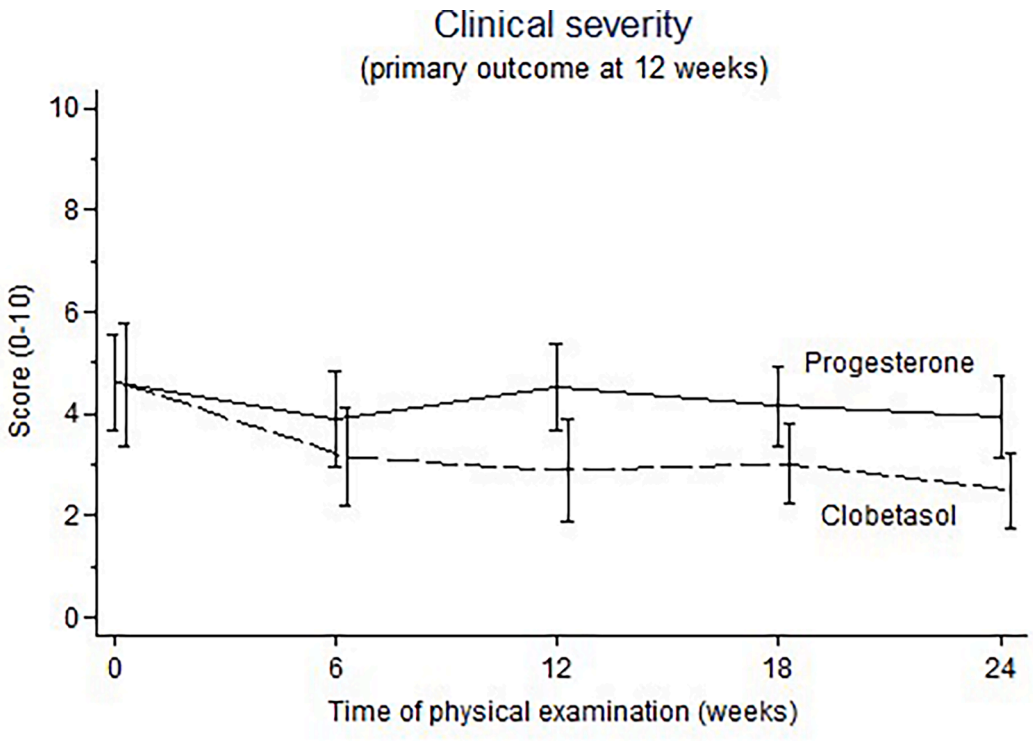


**Fig. 2a.** Physician-administered clinical severity LS score (means with 95% confidence intervals) over time by intervention group.

maintenance therapy; the clinical severity improved over time when using clobetasol proprionate as opposed to progesterone.

*Strengths and limitations*

To our knowledge, this is the first randomized trial to evaluate treatment response in previously untreated premenopausal women with vulvar LS. The most important limitations are that this was a pilot trial powered to detect a large effect of the experimental intervention and that the low recruitment rate led to premature termination of the trial before the planned number of patients was included. However, the standard deviation of the clinical LS score was considerably lower than anticipated in the sample size consideration, which substantially increased the statistical precision of estimates in our analysis. Despite its pilot nature and limited sample size, our trial therefore unequivocally indicates the inferiority of the experimental progesterone 8% ointment as compared with the standard of topical clobetasol, with a 95% confidence interval that rules out the possibility of a clinically relevant benefit. Diagnosis of early onset LS is a challenge for dermatopathologists and only 37 were confirmed positive for LS [34]. Some patients might have presented with Lichen planus instead of LS, or a combination, and it is not always possible to distinguish between them [27]. But the failure to distinguish does not pose much problem, since symptoms, etiology, and treatment options of Lichen planus are almost similar to LS.

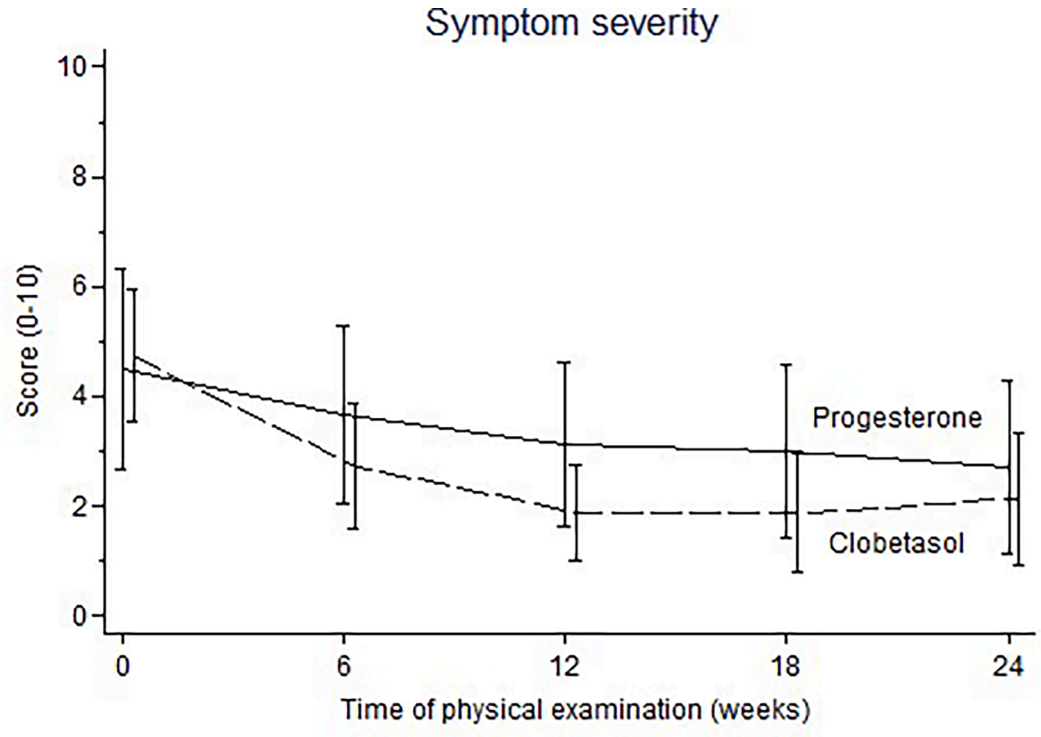


**Fig. 2b.** Patient-administered symptom severity LS score (means with 95% confidence intervals) over time by intervention group.

| | Progesterone N=17 | Clobetasol N=20 | Graph | Difference (95% CI) | P-value for interaction |
|---|---|---|---|---|---|
| **Clinical score at 12 weeks (primary outcome)** | | | | | |
| **Age** | | | | | 0.117 |
| ≤35 years | n=10 | n=10 | | 0.91 (-0.53 to 2.35) | |
| >35 years | n=7 | n=10 | | 2.69 (0.67 to 4.71) | |
| **BMI** | | | | | 0.215 |
| ≤25 | n=15 | n=11 | | 1.115 (-0.60 to 2.83) | |
| >25 | n=2 | n=9 | | 2.50 (0.62 to 4.38) | |
| **Duration of complaints** | | | | | 0.753 |
| ≤1 year | n=7 | n=5 | | 1.173 (-1.64 to 3.99) | |
| >1 year | n=10 | n=15 | | 1.70 (0.22 to 3.17) | |
| **Symptom severity** | | | | | 0.120 |
| Score ≤5 | n=8 | n=12 | | 0.744 (-0.98 to 2.47) | |
| Score >5 | n=9 | n=8 | | 2.53 (0.75 to 4.31) | |
| **Clinical severity** | | | | | 0.194 |
| Score ≤5 | n=11 | n=12 | | 2.20 (0.72 to 3.68) | |
| Score >5 | n=6 | n=8 | | 0.26 (-2.36 to 2.89) | |



**Fig. 3a.** Subgroup analysis for the physician-administered clinical severity LS score.

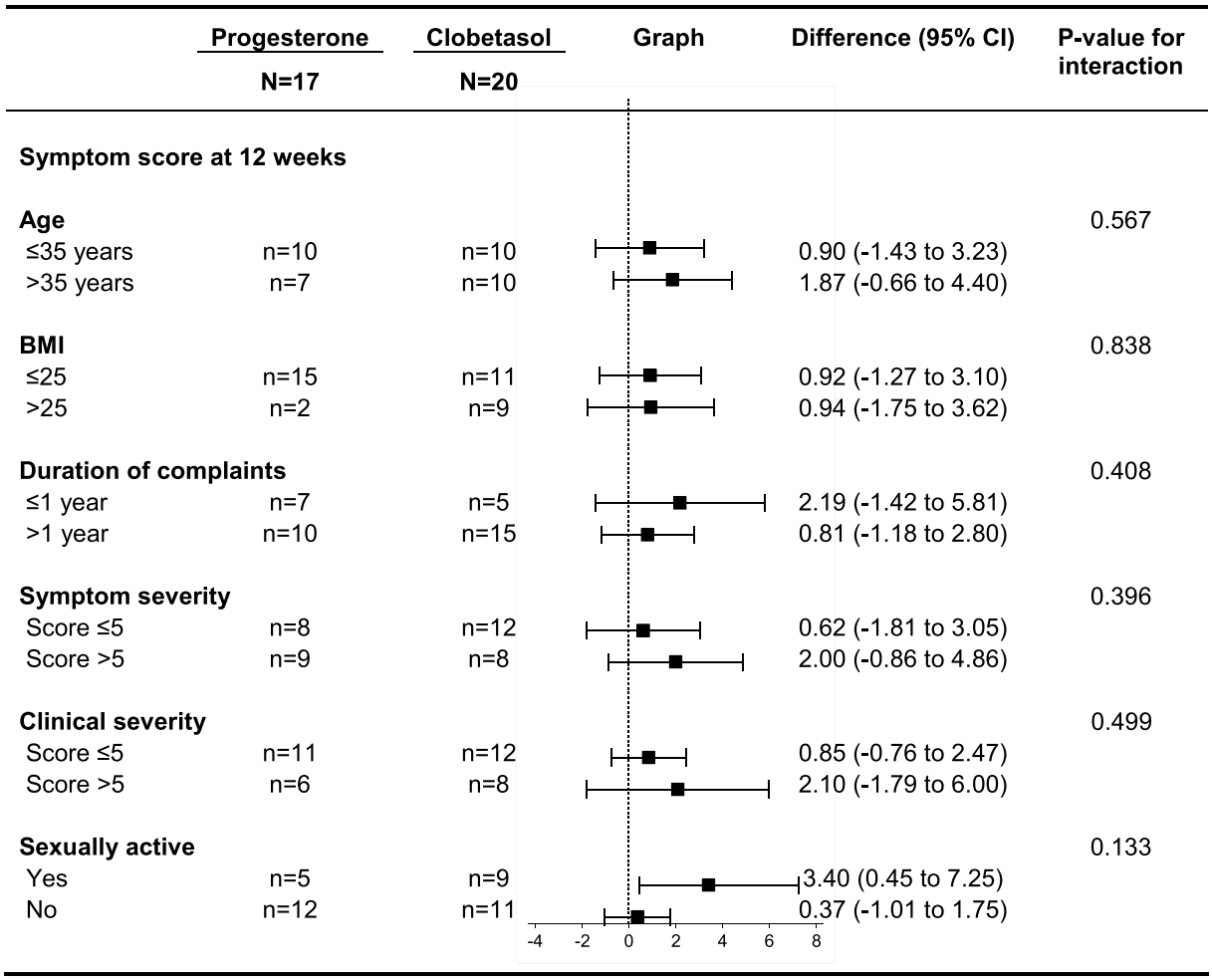


**Fig. 3b.** Subgroup analysis for the patient-administered symptom severity LS score.

**Table 3**
Patients with adverse events (AE) during and up to 28 days after end of treatment.

| | Progesterone (N = 17) | Clobetasol (N = 20) | P value* |
|---|---|---|---|
| | Patient no. (%) ** | Patient no. (%) ** | |
| **Type of Event** | | | |
| Genital herpes | 0 (0%) | 2 (10%) | 0.489 |
| Mycotic infection of vulva and/or labia | 1 (6%) | 1 (5%) | 1.000 |
| Vulvitis | 2 (12%) | 0 (0%) | 0.204 |
| Urinary tract infection | 1 (6%) | 2 (10%) | 1.000 |
| Peritonitis (SAE) | 1 (6%) | 0 (0%) | 0.459 |
| Complaints following vulvovaginal biopsy | 1 (6%) | 1 (5%) | 1.000 |
| Any AE | 4 (24%) | 4 (20%) | 1.000 |
| Drop out due to AE | 2 (12%) | 0 (0%) | 0.204 |
| **Highest severity of AE** | | | |
| Mild (grade 1) | 1 (6%) | 0 (0%) | 0.459 |
| Moderate (grade 2) | 1 (6%) | 4 (20%) | 0.348 |
| Severe (grade 3) | 1 (6%) | 0 (0%) | 0.459 |
| Life-threatening (grade 4) | 1 (6%) | 0 (0%) | 0.459 |
| AE of grade $\geq 3$ | 2 (12%) | 0 (0%) | 0.204 |
| Any serious AE (SAE) | 1 (6%) | 0 (0%) | 0.459 |

* P-value from Fisher's exact test, ** Data are number of patients with event (%).

## Conclusions

Topical progesterone 8% ointment is inferior to standard therapy with topical clobetasol propionate 0.05% in previously untreated premenopausal women with vulvar LS after 12 weeks treatment.

## Role of the funding source

The study was funded by a grant of the Swiss National Science Foundation (SNSF, No. 135568). The funding source had no involvement in study planning, conduct, analysis, interpretation, and publication.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejogrb.2022.03.020.

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