

Systematic review and meta-analysis of randomized controlled trials on topical interventions for genital lichen sclerosis

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Background: Lichen sclerosis (LS) is a chronic inflammatory dermatosis that occurs mainly in the anogenital area and causes itching and soreness. Progressive destructive scarring may result in burying of the clitoris in females and phimosis in males. Affected people have an increased risk of genital cancers.

Objective: We sought to assess the effects of topical interventions for genital LS.

Methods: We undertook a systematic review and meta-analysis using the methodology of the Cochrane Collaboration.

Results: We included 7 randomized controlled trials with a total of 249 participants covering 6 treatments. Clobetasol propionate 0.05% was better than placebo in treating genital LS (participant-rated improvement/remission of symptoms: risk ratio 2.85 [95% confidence interval (CI) 1.45-5.61]; investigator-rated global degree of improvement: standardized mean difference [SMD] 5.74 [95% CI 4.26-7.23]) as was mometasone furoate 0.05% (change in clinical grade of phimosis: SMD -1.04 [95% CI -1.77 to -0.31]). We found no evidence supporting the efficacy of topical androgens and progesterone. There were no differences between pimecrolimus and clobetasol propionate in relieving symptoms through change in pruritus (SMD -0.33 [95% CI -0.99 to 0.33]) and burning/pain (SMD 0.03 [95% CI -0.62 to 0.69]). However, pimecrolimus was less effective than clobetasol propionate in improving gross appearance (investigator-rated global degree of improvement: SMD -1.64 [95% CI -2.40 to -0.87]).

Limitations: Most of the included studies were small.

Conclusions: The current limited evidence supports the efficacy of clobetasol propionate, mometasone furoate, and pimecrolimus in treating genital LS. Further randomized controlled trials are needed. (J Am Acad Dermatol 10.1016/j.jaad.2012.02.044.)

Key words: clobetasol propionate; corticosteroid; dihydrotestosterone; lichen sclerosis; meta-analysis; mometasone furoate; pimecrolimus; progesterone; systematic review; testosterone.

Lichen sclerosis (LS) is a chronic inflammatory dermatosis that occurs mainly in the anogenital area and causes itching and pain. In

women and girls, postinflammatory scarring may cause fusion of the labia minora, narrowing of the vaginal introitus, and burying of the clitoris, resulting

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in dyspareunia, sexual dysfunction, and anal or genital bleeding. LS in men and boys usually occurs on the glans penis and/or foreskin, and may cause phimosis and painful erection. Meatal stenosis may lead to problems passing urine and urinary obstruction. The prevalence is estimated to be between 1:30 and 1:1000 in adults.^{1,2}

The cause of LS is unknown, but there is a strong association with autoimmune diseases, eg, thyroid disease, alopecia areata, vitiligo, and pernicious anemia.³ Up to 74% of affected people had circulating autoantibodies.⁴ An increased incidence of autoantibodies to the extracellular matrix protein 1 was found in people with LS, which supports an autoimmune cause.⁵ In addition, there is evidence of both autoantibody and T-cell reactivity to basement membrane proteins.^{6,7} The high incidence of LS in postmenopausal women suggests a pathogenic role of reduced estrogen levels; however, a protective effect from estrogens, ie, women before menopause will not develop LS, has not been observed.^{2,8} In men, a cause of chronic exposure of a susceptible epithelium to urine as a result of naviculomeatal dysfunction and urinary incontinence in the uncircumcised has been proposed.⁹ Genetic factors are implicated, and cases of familial LS have been reported.¹⁰ Immunogenetic studies have demonstrated a significant association with HLA class II antigen DQ7 and DRB1*12.^{11,12}

LS has a tremendous impact on the quality of life by interfering with function (particularly sexual function) and self-image, and the resultant distress and anxiety are immediately apparent. Many affected people feel embarrassed; some have persistent itching and pain (despite successful control of the inflammation), and many are concerned about how the disorder may progress. The lifetime risk of the development of squamous cell carcinoma in women and men with genital LS is estimated to be 4% to 5%.^{8,13,14} Also, vulval verrucous carcinoma has been associated with LS.¹⁵

There is no cure for LS; however, there are good outcomes as a result of treating the disease. These include the relief of symptoms and prevention of further anatomic changes (caused by sclerosis and

fusion). Some clinical signs may be reversed, but any scarring that has occurred will remain.^{16,17} It is possible that treatments may prevent malignant transformation, but this needs to be evaluated. However, reactivation of latent human papillomavirus infection has been found after topical corticosteroid therapy, which may increase the risk of vulval cancer and requires close follow-up.¹⁸

The objective of this study was to evaluate the level and quality of available evidence regarding the efficacy and reported adverse effects of topical interventions for genital LS, and to identify gaps in knowledge that require further research.

METHODS

We undertook a systematic review and meta-analysis of randomized controlled trials (RCTs) on topical interventions for genital LS following a prespecified protocol according to the methodology of the Cochrane Collaboration.¹⁹ A patient representative assisted us in improving the relevance and readability of this study.

Outcome measures

Primary outcomes included participant-rated improvement/remission of symptoms (in terms of quality of life, pain, itching, and dyspareunia), investigator-rated global degree of improvement (in terms of pallor, purpura, hyperkeratosis, ulceration, erosion, erythema, sclerosis, and scarring), and severe adverse drug reactions (ADRs) (that required withdrawal of treatment, including severe skin irritation or infection). Secondary outcomes included mild ADRs (being not severe enough to require cessation of treatment, eg, mild skin irritation, atrophy, or telangiectasia), duration of remission and/or prevention of subsequent flares, and development of genital squamous cell carcinoma or genital intraepithelial neoplasia. We expressed the results as risk ratios (RR) and 95% confidence intervals (CI) for dichotomous outcomes, and standardized mean difference (SMD) and 95% CI for ordinal outcomes.

Search strategy

We searched 16 databases and trial registers from inception to September 2011 (Table D). We scanned the bibliographies of the included studies, published

CAPSULE SUMMARY

- The current evidence supports the efficacy of clobetasol propionate, mometasone furoate, and pimecrolimus in treating genital lichen sclerosis.
- There is no evidence supporting the use of topical androgens and progesterone in treating genital lichen sclerosis.
- Further randomized controlled trials are needed to determine the optimal potency and regimen of topical corticosteroids, examine other topical interventions, assess the duration of remission or prevention of flares, evaluate the reduction in the risk of genital cancers, and examine the efficacy in improving the quality of the sex lives of people with this condition.

Abbreviations used:

ADR:	adverse drug reaction
CI:	confidence interval
LS:	lichen sclerosus
RCT:	randomized controlled trial
RR:	risk ratio
SMD:	standardized mean difference

reviews, and articles that cited the included studies for relevant studies. There were no language restrictions.

We contacted the trialists of the most recent studies to ask if they knew of any other relevant trials. We did not run separate searches for ADRs, but extracted the data from the included studies.

Data collection and analysis

Two authors independently selected relevant RCTs and extracted the data using a specialized data extraction form. Discrepancies were resolved by discussion with a third author. We contacted the trialists for missing data.

The quality of the included RCTs was assessed for the components listed in Table II. We assessed clinical heterogeneity arising from the study design, interventions, participants, and outcome measures. We assessed statistical heterogeneity using the I^2 statistic. For studies on a similar type of intervention (eg, topical testosterone), we applied meta-analysis using a random effects model to calculate a weighted treatment effect across trials when the I^2 statistic was 80% or less with reasonable clinical homogeneity.

RESULTS

Description of studies

Of 312 citations identified from our search, 7 studies met our inclusion criteria, with a total of 249 participants covering 6 treatments (clobetasol propionate, mometasone furoate, testosterone, dihydrotestosterone, progesterone, and pimecrolimus).²⁰⁻²⁶ One study investigated the effects of testosterone as maintenance therapy.²¹ The details of the included studies are described in Table III. Two included studies were crossover RCTs.^{24,25} The number of participants ranged from 5 to 79.^{20,24,25} Except for one study that recruited boys,²³ all the other 6 studies used adult women as participants.^{20-22,24-26} The setting was either a single hospital or a specialist clinic. All the studies were conducted in either Europe or the United States. The comparator in 5 studies was placebo (vehicle).^{20,21,23,24,26} The other two used an active control: one compared testosterone and dihydrotestosterone,²⁵ whereas the other compared pimecrolimus and clobetasol propionate.²² One study

was supported by a pharmaceutical company.²² The overall quality of included studies was poor (Fig 1).

Effects of interventions

Topical corticosteroids. Only two topical corticosteroids, clobetasol propionate 0.05% (very potent) and mometasone furoate 0.05% ointment (potent), have been assessed.^{20,23}

Clobetasol propionate versus placebo. One study found that topical application of clobetasol propionate for 3 months was significantly better than placebo (participant-rated improvement or remission of symptoms: RR 2.85 [95% CI 1.45-5.61]; investigator-rated global degree of improvement: SMD 5.74 [95% CI 4.26-7.23]) (Fig 2, Analyses 1.1 and 1.2).²⁰ (Fig 2 is available in the Supplemental Materials link associated with the online version of this article at <http://www.jaad.org>). No ADRs occurred in either group.

Mometasone furoate versus placebo. One study compared the efficacy of topical mometasone furoate against placebo after 5 weeks' application.²³ The investigator-rated mean clinical grade of phimosis improved in the mometasone furoate group, but worsened in the placebo group (SMD -1.04 [95% CI -1.77 to -0.31]) (Fig 2, Analysis 2.1). No local or systemic ADRs occurred in either group.

Topical androgens. Two androgens, testosterone propionate 2% cream and dihydrotestosterone 2% cream, were studied in 5 RCTs.^{20,21,24-26}

Testosterone versus placebo. Two RCTs tested the efficacy of testosterone against placebo after application for 3 months and 1 year, respectively.^{20,26} There was no significant difference in the efficacy of testosterone compared with placebo (participant-rated improvement or remission of symptoms: RR 1.21 [95% CI 0.56-2.64] when the two RCTs were combined) (Fig 2, Analysis 3.1). Only one RCT reported the outcome "investigator-rated improvement of gross appearance,"²⁰ and found no significant difference between the two groups (SMD 0.42 [95% CI -0.21 to 1.06]) (Fig 2, Analysis 3.2). No significant difference in severe ADRs was found between the two groups when the two RCTs were combined (RR 5.19 [95% CI 0.62-43.19]) (Fig 2, Analysis 3.3).

Dihydrotestosterone versus placebo. A very small crossover trial randomized 5 participants to receive either dihydrotestosterone or placebo for 3 months, before switching to the other for 3 months.²⁴ The trial lacked a washout period, and a carryover effect appeared in 2 of 3 women who used dihydrotestosterone first. We therefore used only the data from the first period before crossover. No women showed an improvement in their symptoms after either

Table I. Electronic databases and trial registers searched

Electronic databases
Cochrane Skin Group Specialized Register
Cochrane Central Register of Controlled Trials
MEDLINE
EMBASE
Latin American and Caribbean Health Science Information database
Cumulative Index to Nursing and Allied Health Literature
British Nursing Index and Archive
Science Citation Index Expanded
Trial registries
metaRegister of controlled trials
US National Institutes of Health ongoing trials register
World Health Organization International Clinical Trials Registry platform
Australian New Zealand Clinical Trials Registry
Ongoing Skin Trials Register
BIOSIS Previews
Conference Papers Index
Conference Proceedings Citation Index-Science

preparation. No significant difference in investigator-rated improvement of gross appearance was found between dihydrotestosterone and placebo (RR 5.25 [95% CI 0.41-67.73]) (Fig 2, Analysis 4.1).

Testosterone versus clobetasol propionate. One RCT found that after 3 months' application, testosterone was significantly less effective than clobetasol propionate (participant-rated improvement or remission of symptoms: RR 0.67 [95% CI 0.45-0.98]; investigator-rated global degree of improvement: SMD -1.81 [95% CI -2.56 to -1.06]) (Fig 2, Analyses 5.1 and 5.2).²⁰ No significant differences were found between the two groups in severe ADRs (RR 3.00 [95% CI 0.13-69.52]) or mild ADRs (RR 7.00 [95% CI 0.38-127.32]) (Fig 2, Analyses 5.3 and 5.4).

Testosterone versus dihydrotestosterone. A very small crossover trial randomized 5 participants to receive either testosterone or dihydrotestosterone for 3 months, before switching to the other for 3 months.²⁵ The trial lacked a washout period, and we used only the data from the first period before crossover for analysis. The trial did not find significant differences in efficacy between the two androgens (participant-rated remission of itching: RR 0.25 [95% CI 0.01-4.23]; investigator-rated gross improvement: RR 1.00 [95% CI 0.53-1.87]) (Fig 2, Analyses 6.1 and 6.2).

Testosterone versus placebo as maintenance therapy. A study investigated whether topical testosterone could control the symptoms and signs of vulval LS after an initial 24-week treatment with clobetasol propionate 0.05% cream.²¹ The study

Table II. Quality assessment of included studies

1. Method of randomization
2. Allocation concealment
3. Blinding
4. Incomplete outcome data
5. Selective reporting
6. Degree of certainty of diagnosis of LS
7. Baseline characteristics of participants
8. Administering of interventions (drug identity, source, dose, duration of treatments, and adequacy of instructions)
9. Standardization of outcome assessment
10. Discontinuation of previous treatments
11. Previous and concomitant treatments for LS
12. Use and appropriateness of statistical analyses where tabulated data could not be extracted from original publication

LS, Lichen sclerosis.

found that testosterone when used as maintenance therapy for 24 weeks worsened the symptoms ($P < .05$), whereas the vehicle-based placebo caused no change in symptoms or gross appearance (Fig 2, Analyses 7.1 and 7.2). No severe ADRs occurred in both groups. There was no significant difference in mild ADRs between the two groups (RR 9.00 [95% CI 0.52-154.56]) (Fig 2, Analysis 7.3).

Topical progesterone. One study found no difference in efficacy between progesterone 2% cream and placebo after 3 months' application (participant-rated improvement/remission of symptoms: RR 1.58 [95% CI 0.72-3.50]; investigator-rated global degree of improvement: SMD 0.34 [95% CI -0.29 to 0.97]) (Fig 2, Analyses 8.1 and 8.2).²⁰

Pimecrolimus. One study tested the effects of pimecrolimus 1% cream against clobetasol propionate 0.05% cream after 12 weeks' application.²² Both were effective in relieving pruritus and burning/pain, and there were no significant differences between pimecrolimus and clobetasol propionate in relieving pruritus and burning/pain (change in pruritus: SMD -0.33 [95% CI -0.99 to 0.33]; change in burning/pain: SMD 0.03 [95% CI -0.62 to 0.69]) (Fig 2, Analyses 9.1 and 9.2). Investigator Global Assessment showed both preparations were effective. However, pimecrolimus was less effective than clobetasol propionate (investigator-rated global degree of improvement: SMD -1.64 [95% CI -2.40 to -0.87]) (Fig 2, Analysis 9.3). No ADRs occurred in either group.

DISCUSSION

The current evidence supports the efficacy of clobetasol propionate 0.05% and mometasone

Table III. Characteristics of studies

Study	Participants	Interventions	Outcomes reported in trials	Notes
Bracco et al, ²⁰ 1993	79 Women with long-standing, biopsy-proven vulval LS Mean age = 57 y (range 27-83) Mean duration of disease = 33 mo (range 2-120)	4 Topical drugs including the following: A: Testosterone (2%); B: Progesterone (2%); C: Clobetasol propionate (0.05%); and D: Placebo (a cream-based preparation) All topical drugs were applied twice daily for 3 mo, except clobetasol propionate, which was applied twice daily for 1 mo then once daily for 2 mo	(1) Symptoms (itching, burning, pain, and dyspareunia) (2) Gross appearance (hyperkeratosis, purpura, thickness of plaques, atrophy, and erosions) (3) Histologic features (epidermal atrophy, edema, intensity of inflammatory infiltrate, and fibrosis) All were classified according to 0- to 3-point scoring system	Setting: university hospital Country: Italy Funding source: not reported
Cattaneo et al, ²¹ 1996	32 Women with biopsy-proven vulval LS after 24 wk of treatment with 0.05% clobetasol propionate cream Mean age = 60 y, median age = 58 (range 28-85) Mean duration of disease = 22.7 mo (range 2-96) 28 Women (87.5%) were postmenopausal	A: Testosterone propionate 2% B: Placebo (petrolatum vehicle alone) These were taken once daily as maintenance therapy for 24 wk	(1) Symptoms (itching, burning, soreness, and dryness) (2) Gross aspects (hyperkeratosis, atrophy, and sclerosis) (3) Histologic features (epidermal atrophy, edema, inflammatory infiltrate, and fibrosis) All were evaluated using 0- to 3-point scoring system	Setting: university hospital Country: Italy Funding source: not reported
Goldstein et al, ²² 2011	38 Women with biopsy-proven vulval LS	A: Pimecrolimus cream 1% twice daily B: Alternate clobetasol cream 0.05% (in evening) and vehicle cream (in morning) These were used for 12 wk	Primary outcomes of trial (1) Histopathologic change in inflammation (0-to-4 scale) Secondary outcomes of trial (1) Change from baseline in PR (VAS-PR) and BP (VAS-BP) rated by participants using 0- to 10-point VAS questionnaires (2) Investigator Global Assessment of severity of disease (0-to-3 scale), clinical evaluation of lichenification (0-to-3 scale), and clinical valuation of ulceration/fissuring (0-to-3 scale)	Setting: specialist clinic (Center for Vulvovaginal Disorders) Country: United States Funding source: Novartis Pharmaceuticals Co

Continued

Table III. Cont'd

Study	Participants	Interventions	Outcomes reported in trials	Notes
Kiss et al, ²³ 2001	40 Boys with penile LS	A: Mometasone furoate 0.05% ointment B: Placebo once daily These were taken for 5 wk	Clinical score of phimosis (1-to-4 grade)	Setting: children's hospital Country: Hungary Funding source: not reported
Paslin ²⁴ 1991	5 Women with biopsy-proven vulval LS	Randomized crossover trial A: Dihydrotestosterone 2% B: Placebo (white petrolatum vehicle) These were taken twice daily for 3 mo, then treatment was reversed for another 3 mo	(1) Subjective symptoms (2) Objective gross improvement (documented by photographs) (3) Histopathologic findings	Setting: private practice Country: United States Funding source: not reported
Paslin ²⁵ 1996	5 Postmenopausal women with biopsy-proven vulval LS	Randomized crossover trial A: Dihydrotestosterone 2% B: Testosterone propionate 2% These were taken twice daily for 3 mo, then treatment was reversed for another 3 mo	(1) Vulval itching (0-to-4 scale) (2) Dyspareunia (presence or absence) (3) Gross appearance (photographic improvement) (4) Histopathologic findings (formation of elastic fibers)	Setting: university hospital Country: United States Funding source: not reported
Sideri et al, ²⁶ 1994	58 Women with histologically confirmed vulval LS	A: Testosterone propionate 2% B: Placebo (petrolatum ointment) These were taken for 1 y	(1) Symptoms (2) Gross appearance (3) Histologic changes	Setting: university hospital Country: Italy Funding source: not reported

BP, Burning/pain; LS, lichen sclerosus; PR, pruritus; VAS, visual analog scale.

furoate 0.05% in treating vulval and penile LS, respectively.^{20,23}

Improvement in gross appearance after topical application of either testosterone or dihydrotestosterone was found, according to the investigators, in a very small crossover trial without placebo control on 5 women (3 women used topical testosterone, and 2 women used topical dihydrotestosterone first).²⁵ However, no improvement in subjective symptoms was observed. Furthermore, two other studies did not find significant efficacy of testosterone in either symptoms or gross appearance.^{20,26} When used as maintenance therapy after initial corticosteroid therapy in another trial, topical testosterone worsened symptoms ($P < .05$), but the placebo did not.²¹ Thus, there is no evidence to support the efficacy of topical androgens. The observed gross changes (eg, clitoral enlargement²⁵) were most likely a result of their virilizing effect. There is also no evidence to support the efficacy of another topical sex hormone, progesterone.²⁰

The current evidence found no differences between pimecrolimus and clobetasol propionate in reducing pruritus (SMD -0.33 [95% CI -0.99 to 0.33]) and burning/pain (SMD 0.03 [95% CI -0.62 to 0.69]). However, clobetasol propionate was only applied once daily in this trial.²² Thus, the comparable efficacy of pimecrolimus might have been overestimated. On the other hand, pimecrolimus was less effective than clobetasol propionate when assessed by investigators (investigator-rated global degree of improvement: SMD -1.64 [95% CI -2.40 to -0.87]). Furthermore, clobetasol propionate was superior to pimecrolimus in improving inflammation ($P = .015$).²²

All but one RCT enrolled adult women with vulval LS as participants.^{20-22,24-26} Only one RCT enrolled boys with penile LS as participants.²³ This limitation may compromise the external validity of the evidence.

Only two topical corticosteroids, clobetasol propionate and mometasone furoate, have been tested

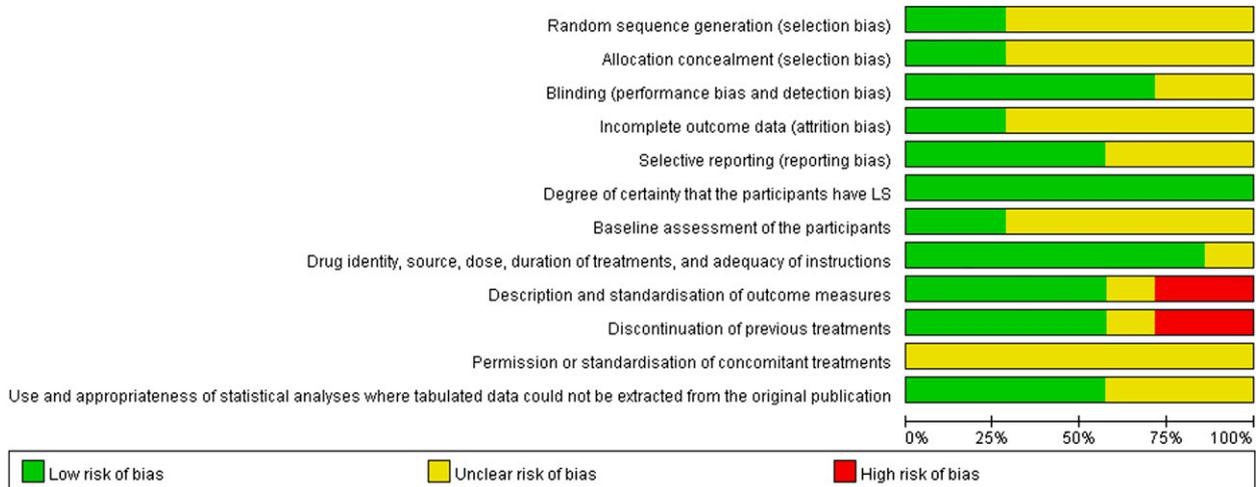


Fig 1. Methodological quality of included studies. *LS*, Lichen sclerosis.

in RCTs.^{20,23} The concentration of mometasone furoate used was 0.05%,²³ which was half the usual concentration of 0.1%. It is unclear whether other potent or moderate topical corticosteroids are also effective.

The regimen of clobetasol propionate varied among the RCTs. In one trial,²⁰ clobetasol propionate 0.05% was applied twice daily for 1 month then once daily for 2 months. In another trial comparing pimecrolimus and clobetasol propionate, clobetasol propionate was applied once daily.²² There are no RCTs comparing the efficacy of different regimens of topical clobetasol propionate in treating genital LS.

Pimecrolimus was effective in treating genital LS,²² but is only licensed for atopic dermatitis and not indicated for use in children younger than 2 years of age.²⁷

Conclusions

Implications for practice. The evidence supports that topical clobetasol propionate and mometasone furoate are effective in treating vulval and penile LS, respectively. It is unclear whether other topical corticosteroids are effective. There is no evidence supporting the use of topical androgens and progesterone in treating genital LS. The current evidence found no significant difference between pimecrolimus and clobetasol propionate in the efficacy of relieving symptoms, but pimecrolimus is less effective than clobetasol propionate in improving gross appearance and reducing inflammation.

Implications for research. The current evidence is limited, and further studies are required to fill in gaps in knowledge. First, we need RCTs determining the potency and regimen (eg, frequency and duration of application) of topical

corticosteroids that have adequate therapeutic efficacy but with the least desirable adverse effects (eg, infections and atrophy). Second, only a limited number of topical interventions (eg, topical corticosteroids), sex hormones, and pimecrolimus have been tested. RCTs testing other interventions (eg, topical tacrolimus) are needed. Third, one of our secondary outcomes, “duration of remission or prevention of subsequent flares,” should be included in future RCTs, although this means that long follow-up periods are required. Fourth, it remains unknown whether effective treatments can reduce the risk of development of genital squamous cell carcinoma or genital intraepithelial neoplasia from LS. RCTs of adequate length and sample size to answer this question should be conducted. Last but not least, the quality of the sex lives of people with genital LS should be examined in future trials.

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REFERENCES

- Liebovitz A, Kapulun V, Saposhnicov N, Habet B. Vulvovaginal examinations in elderly nursing home women residents. *Arch Gerontol Geriatr* 2000;31:1-4.
- Tasker GL, Wojnarowska F. Lichen sclerosis. *Clin Exp Dermatol* 2003;28:128-33.
- Meyrick Thomas RH, Ridley CM, McGibbon DH, Black MM. Lichen sclerosis et atrophicus and autoimmunity—a study of 350 women. *Br J Dermatol* 1988;118:41-6.
- Harrington CI, Dunsmore IR. An investigation into the incidence of auto-immune disorders in patients with lichen sclerosis and atrophicus. *Br J Dermatol* 1981;104:563-6.
- Oyama N, Chan I, Neill SM, Hamada T, South AP, Wessagowit V, et al. Autoantibodies to extracellular matrix protein 1 in lichen sclerosis. *Lancet* 2003;362:118-23.
- Baldo M, Bailey A, Bhogal B, Groves RW, Ogg G, Wojnarowska F. T cells reactive with the NC16A domain of BP180 are present

- in vulval lichen sclerosus and lichen planus. *J Eur Acad Dermatol Venereol* 2010;24:186-90.
7. Howard A, Dean D, Cooper S, Kirtschig G, Wojnarowska F. Circulating basement membrane zone antibodies are found in lichen sclerosus of the vulva. *Australas J Dermatol* 2004;45:12-5.
 8. Powell JJ, Wojnarowska F. Lichen sclerosus. *Lancet* 1999;353:1777-83.
 9. Bunker CB. Comments on the British Association of Dermatologists guidelines for the management of lichen sclerosus. *Br J Dermatol* 2011;164:894-5.
 10. Sherman V, McPherson T, Baldo M, Salim A, Gao XH, Wojnarowska F. The high rate of familial lichen sclerosus suggests a genetic contribution: an observational cohort study. *J Eur Acad Dermatol Venereol* 2010;24:1031-4.
 11. Marren P, Yell J, Charnock FM, Bunce M, Welsh K, Wojnarowska F. The association between lichen sclerosus and antigens of the HLA system. *Br J Dermatol* 1995;132:197-203.
 12. Gao XH, Barnardo MC, Winsey S, Ahmad T, Cook J, Agudelo JD, et al. The association between HLA DR, DQ antigens, and vulval lichen sclerosus in the UK: HLA DRB112 and its associated DRB112/DQB10301/04/09/010 haplotype confers susceptibility to vulval lichen sclerosus, and HLA DRB10301/04 and its associated DRB10301/04/DQB10201/02/03 haplotype protects from vulval lichen sclerosus. *J Invest Dermatol* 2005;125:895-9.
 13. Wallace HJ. Lichen sclerosus et atrophicus. *Trans St Johns Hosp Dermatol Soc* 1971;57:9-30.
 14. Nasca MR, Innocenzi D, Micali G. Penile cancer among patients with genital lichen sclerosus. *J Am Acad Dermatol* 1999;41:911-4.
 15. Wang SH, Chi CC, Wong YW, Salim A, Manek S, Wojnarowska F. Genital verrucous carcinoma is associated with lichen sclerosus: a retrospective study and review of the literature. *J Eur Acad Dermatol Venereol* 2010;24:815-9.
 16. Cooper SM, Gao XH, Powell JJ, Wojnarowska F. Does treatment of vulvar lichen sclerosus influence its prognosis? *Arch Dermatol* 2004;140:702-6.
 17. Renaud-Vilmer C, Cavelier-Balloy B, Porcher R, Dubertret L. Vulvar lichen sclerosus: effect of long-term topical application of a potent steroid on the course of the disease. *Arch Dermatol* 2004;140:709-12.
 18. von Krogh G, Dahlman-Ghozlan K, Syrjänen S. Potential human papillomavirus reactivation following topical corticosteroid therapy of genital lichen sclerosus and erosive lichen planus. *J Eur Acad Dermatol Venereol* 2002;16:130-3.
 19. Chi CC, Baldo M, Kirtschig G, Brackenbury F, Lewis F, Wojnarowska F. Topical interventions for genital lichen sclerosus (protocol). *Cochrane Database Syst Rev* 2010;1:CD008240.
 20. Bracco GL, Carli P, Sonni L, Maestrini G, De Marco A, Taddei GL, et al. Clinical and histologic effects of topical treatments of vulval lichen sclerosus: a critical evaluation. *J Reprod Med* 1993;38:37-40.
 21. Cattaneo A, Carli P, De Marco A, Sonni L, Bracco G, De Magnis A, et al. Testosterone maintenance therapy: effects on vulvar lichen sclerosus treated with clobetasol propionate. *J Reprod Med* 1996;41:99-102.
 22. Goldstein AT, Creasey A, Pfau R, Phillips D, Burrows LJ. A double-blind, randomized controlled trial of clobetasol versus pimecrolimus in patients with vulvar lichen sclerosus. *J Am Acad Dermatol* 2011;64:e99-104.
 23. Kiss A, Csontai A, Pirot L, Nyirady P, Merksz M, Kiraly L. The response of balanitis xerotica obliterans to local steroid application compared with placebo in children. *J Urol* 2001;165:219-20.
 24. Paslin D. Treatment of lichen sclerosus with topical dihydrotestosterone. *Obstet Gynecol* 1991;78:1046-9.
 25. Paslin D. Androgens in the topical treatment of lichen sclerosus. *Int J Dermatol* 1996;35:298-301.
 26. Sideri M, Origoni M, Spinaci L, Ferrari A. Topical testosterone in the treatment of vulvar lichen sclerosus. *Int J Gynaecol Obstet* 1994;46:53-6.
 27. Chi CC, Wang SH, Charles-Holmes R, Ambros-Rudolph C, Powell J, Jenkins R, et al. Pemphigoid gestationis: early onset and blister formation are associated with adverse pregnancy outcomes. *Br J Dermatol* 2009;160:1222-8.