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ORIGINAL RESEARCH ARTICLE

Long-term consequences of juvenile vulvar lichen sclerosus: A cohort study of adults with a histologically confirmed diagnosis in childhood or adolescence

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Abstract

Introduction: Vulvar lichen sclerosus (VLS) occurs in at least one in 900 girls. There is limited knowledge as to what extent the disease persists in adulthood and what the repercussions in adulthood may be. The aim of this study is to evaluate the long-term consequences of VLS diagnosed in childhood or adolescence.

Material and methods: The population of females histologically diagnosed with VLS in childhood or adolescence in the Netherlands between 1991 and 2015 was identified through the national pathology database. Histological specimens were retrieved and re-evaluated. Potential participants for whom the diagnosis was reconfirmed and who are now adults, were then traced and surveyed. Descriptive statistics were calculated and compared with the literature. Main outcome measures are the demographics of the cohort, their scores on standardized quality of life (QoL) and sexuality questionnaires and answers to additional questions regarding patients' experience with the disease. The questionnaires used were the Dermatology Life Quality Index (DLQI), the Skindex-29, the Female Sexual Function Index (FSFI) and the Female Sexual Distress Scale-Revised (FSDS-R). Secondary outcome measures include obstetric history and histological features found in the original tissue specimens.

Results: A total of 81 women participated, median age 29.0 years, median follow-up from childhood diagnosis 19.5 years. Both QoL and sexuality were somewhat affected in 51.9% of cases. Less than half (45%) reported having regular check-ups. Forty-five (56%) reported symptoms within the past year; of those with symptoms, 14 (31%) were not under surveillance. Cesarean section rate (14.5%) was comparable to the

Abbreviations: DLQI, Dermatology Life Quality Index; FSDS-R, Female Sexual Distress Scale-Revised; FSFI, Female Sexual Function Index; IQR, interquartile range; JVLS, juvenile vulvar lichen sclerosus; LS, lichen sclerosus; OASIS, obstetric anal sphincter injuries; PALGA, Pathologisch-Anatomisch Landelijk Geautomatiseerd Archief; Dutch Pathology Registry; QoL, quality of life; SKINDEX-29, Health-related quality of life questionnaire with 29 questions; VLS, vulvar lichen sclerosus.

[†]Participants in the Steering Group-JVLS are listed in Appendix A.

general population, and there were more high-grade obstetric anal sphincter injuries with vaginal deliveries than expected. Sixteen respondents (20%) were not aware of the childhood diagnosis prior to this study.

Conclusions: Symptoms due to VLS are reported by most adults diagnosed as juveniles. QoL and sexuality are affected and correlate to recent symptoms. VLS as a juvenile does not preclude a vaginal delivery. Women diagnosed with VLS in childhood or adolescence are often lost to follow-up.

KEYWORDS
adolescent lichen sclerosus, DQLI, FSDS-R, FSFI, juvenile vulvar lichen sclerosus, pediatric lichen sclerosus, quality of life, sexual well-being, Skindex-29, vulvar lichen sclerosus

1 | INTRODUCTION

Genital lichen sclerosus (LS) may appear at any age, with incidence varying with age and sex.[1] Vulvar lichen sclerosus (VLS) is often considered to be a disease of the elderly.[1] The incidence of VLS is often said to be bimodal, with the diagnosis being more likely in prepuberty, affecting at least one in 900 girls, and in the post-menopausal phase, affecting up to one in 30 elderly women.[1,2] However, exact statistics are unknown and Kirtschig reports that 50% of females with VLS are affected before the menopause.[2] A population study from Finland, in comparison, reported that 21.8% of cases of VLS were diagnosed before 50 years of age, with 4.1% of cases being diagnosed in 0 to 19-year-olds.[3]

When VLS is diagnosed in a juvenile (in childhood or adolescence), at a time when the vulva is still developing, an additional dimension is added to the questions that may arise. Will the VLS affect the vulva in its evolution, and will it persist into adulthood? Does this diagnosis when made at such an early age affect self-image and quality of life (QoL)?

The long-term sequelae of juvenile vulvar lichen sclerosus (JVLS) have not yet been sufficiently clarified.[4] One study of 46 prepubertal females with JVLS, with an average follow-up of 2.7 years,[5] showed that proper treatment and adherence to a maintenance regimen halts progression and scarring and protects against relapses, though architectural changes that have already taken place are irreversible. Lagerstedt et al.[6] showed that after puberty and beyond, these children often do not continue treatment and are commonly lost to follow-up. For the adults in Lagerstedt's survey, the VLS affected QoL in 67% (9/15).[6] In a recent retrospective chart study by Winfrey et al.[7] of 26 prepubertal girls, 10 (38.5%) continued to have symptoms after menarche.

The primary aim of this study is to determine how often LS that developed in childhood or adolescence persists in adulthood, and to what extent the disease has an impact on QoL and sexuality for this specific group of adults. A secondary aim is to study potential repercussions of VLS on obstetric outcome and to relate findings in the childhood biopsies to current symptoms. To elucidate the long-term repercussions of JVLS, ideally one would follow patients from the time of diagnosis in childhood or adolescence well into adulthood, yielding results only after several decades. We sought to approximate this ideal in a timely manner, studying a cohort of adult females who as juveniles had had a confirmed diagnosis of VLS regardless of the current status of their disease. This information may help patients diagnosed with JVLS, their parents and the professionals who are involved in counseling.

Key message

Less than half of those diagnosed with vulvar lichen sclerosus in childhood or adolescence remain under surveillance as adults, even when the disease currently affects their quality of life and sexuality. One-fifth were not even aware of the childhood diagnosis.

2 | MATERIAL AND METHODS

Through the Dutch Nationwide Pathology Databank (PALGA) all vulva biopsies classified as LS in females ≤18 years old in between 1991 and 2015 were identified. JVLS is defined as VLS occurring in childhood or adolescence up to the age of 18. Slides and tissue samples were requested from pathology laboratories throughout The Netherlands.

2.1 | Histological analysis

Histological material was anonymously retrieved. Revision by two expert pathologists, a gynecopathologist and a dermatopathologist, was performed using the systematic and semiquantitative method as previously described.[8] Forty-eight histological characteristics were scored, describing features and severity of LS. Exclusion criteria were: inconclusive histological review, quality of the tissue sample too poor or the presence of a concomitant lesion such as a nevus which may affect the microscopic interpretation of LS.[9] All cases with a histologically confirmed diagnosis were then included if the person was an adult (≥18 years old) as of 1 January 2021.

2.2 | Recruitment

For each case, the pathology laboratory that had supplied the specimens, contacted the local physician, who then identified the patient. This physician checked that the clinical information corresponded to the histological diagnosis before tracing the person. The name and contact information were shared with the research team only after approval by the participant. The participant then received comprehensive study information, and informed consent was requested. Separately, consent was sought to link the questionnaires to the thus far anonymous tissue sample from the vulvar biopsy performed in childhood.

Recruitment and inclusion occurred from January through October 2021.

2.3 | Questionnaires

Participants completed an online questionnaire with five components, including four validated questionnaires: the Dermatology Life Quality Index (DLQI),[10] Skindex-29,[11] Female Sexual Function Index (FSFI)[12] and the Female Sexual Distress Scale-Revised (FSDS-R).[13,14]

The DLQI is a dermatology-specific QoL questionnaire with 10 questions with a 4-point Likert-type scale for which the total score is the sum of these 10 items, range 0–30, a higher score implying greater impact. The Skindex-29 is a dermatology-specific QoL questionnaire with 29 questions in three domains – symptoms, emotions, functioning – each on a 5-point scale. The domain score is the average of the score per item, and the total score the average of the domain scores, range 0–100, a higher score reflecting greater impact. The FSFI has 19 questions covering six subscales – desire, arousal, lubrication, orgasm, satisfaction, pain. Each question is answered on a 5-point Likert-type scale; domain scores are weighed and added-up, with a total score range 2.0–36.0. A score of 26.55 or less signifies sexual dysfunction. The FSDS-R encompasses 13 questions, and is scored using a 5-point Likert-type scale. The total score is the sum, range 0–52; a score of 11 or greater indicates sexually related personal distress.

The fifth part included questions about the participant's past and present experience with (J)VLS as well as a short gynecologic, obstetric and family history (Table S1). Part 5 also included open-ended questions in which the participants could elaborate on their experience with LS and their participation in the study. Answers to the questionnaires and histology analysis of the participants were stored using the LIMESURVEY and GEMSTRACKER software.

2.4 | Statistical analyses

Analysis was performed using IBM SPSS Statistics, version 28. The results from the validated questionnaires DLQI, Skindex-29, FSFI and FSDS-R were compared with the literature on adult VLS.[15,16] Results are given as median and interquartile range (IQR). Associations between questionnaire scores and age were analyzed using Spearman correlation, and associations between questionnaires and both parity and recent symptoms were analyzed using the Mann–Whitney *U*-test.

Analyses regarding histology were performed using the chi-square test to determine the relation of recent symptoms to histological characteristics seen in the historical biopsies. For individual items, a $P \leq 0.05$ was considered significant. A Dunn–Šidák correction was calculated to correct for multiple testing.

Finally, an inventory was made of recurring themes in the answers to the five open-ended questions.

2.5 | Ethics statement

IRB approval was granted by the Erasmus Medical Center MEC-2019-0474 Netherlands Registry NL63335.078.19 on November 19, 2020. Participants gave their written informed consent.

3 | RESULTS

3.1 | Population characteristics

In all, 328 cases of vulvar biopsies in juveniles (≤18 years old) were registered as VLS in the PALGA database in the period 1991–2015. Histology material was available for 313 cases. Upon revision, 61 cases were excluded. Reasons for exclusion were as follows: analysis was not conclusive for vulvar LS in 30 cases, in eight cases the quality of the tissue sample was too poor, and in 13 cases there was a concomitant lesion. Of the remaining 252 confirmed cases, 32 pertained to females still younger than 18 years old on January 1, 2021. Thus, a cohort of 220 adult women with a definitive histological diagnosis of VLS as a juvenile in the period 1991–2015 was delineated.

Women were not always traceable or deemed eligible by the clinician. In all, 106 people were traced (48%) and were willing to receive comprehensive study information. A total of 81 women (76% of those traced, 37% of the cohort) participated in the study, 80 of whom completed all five parts, and 80 respondents gave informed consent to link their biopsy to their answers.

No statistically significant differences were found when comparing the participants to the rest of the cohort regarding year of biopsy ($P = 0.165$) or age on January 1, 2021 ($P = 0.789$). Median age at time of biopsy was 9.0 years (IQR 5.5–13.5 for respondents and IQR 7.0–13.8 for the rest of the cohort). The median follow-up from date of biopsy to date of completing the online questionnaire was 19.5 years (IQR 13.9–24.2, range 7.1–30.7 years).

3.2 | Clinical history of participants

Median age at time of participation was 29.0 years (IQR 23.5–33.5, range 18–47 years). Table 1 describes patients' retrospective

reporting of signs and symptoms and of treatments received during childhood.

Table 2 shows the answers to the questions on personal or family history, and Table 3 shows current symptoms and experience with VLS. In Table S2A these results are shown alongside what was found in the literature regarding adult-VLS and in the general population.[2,17–20] Of the respondents with symptoms within the past year, one-third (14 of 45) were not being treated. There were 31 respondents (39%) who had been pregnant, with collectively 55 ongoing pregnancies. In three of the eight cesarean sections, the respondent reported opting for an elective surgical birth because of the VLS. There were four obstetric anal sphincter injuries (OASIS) reported (7.3% of the pregnancies), two of which were reported by one participant. Auto-immune disease was reported by eight respondents (10%).

TABLE 1 Retrospective reporting of signs and symptoms and of treatments received during childhood in 80 adult women diagnosed with juvenile vulvar lichen sclerosus. (median age 9.0 years at time of biopsy).

Characteristic[a]	*n* (%)
Presenting symptoms	
Itching	66 (82.5%)
Anatomic changes	46 (57.5%)
Vulvar pain	45 (56.3%)
Difficulties with micturition	27 (33.8%)
Bleeding	18 (22.5%)
Constipation	12 (15.0%)
Abdominal pain	5 (6.3%)
Extragenital lesions	2 (2.5%)
Unknown[b]	4 (5.0%)
Informed of LS at time of biopsy	50 (62.5%)
First-line topical treatment prescribed	53 (66.3%)
Moisturizers prescribed	27 (33.8%)
Maintenance treatment advised	Yes 29 (36.3%), No 19 (23.8%)

Abbreviation: VLS, vulvar lichen sclerosus.

[a]Could not always be recalled.

[b]Response "could not recall" or left blank.

3.3 | Quality of life and sexual function in adulthood

Table 4 gives the results of the DLQI, Skindex-29, FSFI and FSDS-R. Using the DLQI, 51.9% reported some impact of VLS on their QoL and 6.2% reported a large impact. According to the scores of the Skindex-29 in 30.9%, VLS had an effect on QoL, with 9.9% scoring a severe impact. The FSFI demonstrated that 51.9% had sexual dysfunction, and the FSDS-R scores showed that 53.7% had experienced sexual distress. A comparison with the literature on adult VLS[15,16] is given in Table S2B. We analyzed whether scores were associated with age, having ever been pregnant or having experienced symptoms from VLS over the past year. There was no significant association with age. The median age of those who had never been pregnant was 25.0 years (IQR 21.5–29.0) and median age of those who had ever been pregnant was 33.0 years (IQR 31.0–37.0). Having ever been pregnant showed no statistically

TABLE 2 Answers of respondents to questions on gynecological, family and obstetric history.

	Response in questionnaire (*n* = 80, median age 29.0 years)		
	Yes, *n* (%)	No, *n* (%)	Do not know, unanswered or not applicable, *n* (%)
Family and personal history			
Familiar LS	16 (20%)	45 (56%)	19 (24%)
Other auto-immune diseases	8 (10%)	49 (61.3%)	23 (28.7%)
Other auto-immune diseases in the family	12 (15%)	34 (41.5%)	34 (41.5%)
Vulvar cancer	0	80 (100%)	0
Vulvar cancer in the family	1 (1.3%)	58 (72.5%)	21 (26.3%)
Past pregnancies			
Ever pregnant (68 pregnancies, 55 deliveries)	31 (38.8%)	46 (57.5%)	3 (3.8%)
Spontaneous vaginal birth	40 of 55 (72.7%)		
Vaginal assisted birth	7 of 55 (12.7%)		
C-section	8 of 55 (14.5%)		
OASIS	4 of 55 (7.3%)		

Abbreviations: LS, lichen sclerosus; VLS, vulvar lichen sclerosus; OASIS, obstetric anal sphincter injuries.

TABLE 3 Answers of respondents to questions on current symptoms and worries.

	Response in questionnaire ($n=80$, median age 29.0 years)		
	Yes, *n* (%)	**No, *n* (%)**	**Do not know, unanswered or not applicable, *n* (%)**
Regular check-ups for LS	36 (45%)	43 (53.8%)	1 (1.3%)
Find it difficult to follow instructions on ointments	17 (21.3%)	19 (23.8%)	44 (55%)
Symptoms from VLS within last year	45 (56.2%)	34 (42.5%)	1 (1.3%)
Worries about the consequences of VLS	Very much 4 (5%), much 5 (6.3%)	A little 42 (52.5%), not at all 20 (25%)	9 (11.3%)
Able to speak with people you are close to about VLS	Yes 31 (38.8%) somewhat 26 (32.5%)	8 (10%)	15 (18.8%)
Worries about possible (future) consequences of sexual function due to VLS	Very much 6 (7.5%), much 13 (16.3%)	A little 34 (42.5%), not at all 25 (31.3%)	2 (2.5%)

Abbreviations: LS, lichen sclerosus; VLS, vulvar lichen sclerosus.

TABLE 4 Results of DLQI, Skindex-29, FSFI and FSDS-R in 81 adult women with histologically proven juvenile vulvar lichen sclerosus ($n=81$, median age = 29.0 years old).

SCORE	*n* (%)
DLQI	
0–1 no impact	39 (48.1%)
2–5 small impact	27 (33.3%)
6–10 moderate impact	10 (12.3%)
11–20 large impact	5 (6.2%)
>20 extreme impact	0 (0%)
Median (IQR)	2.0 (IQR 0–4.0)
Skindex-29	
0–24 no impact	56 (69.1%)
25–31 small impact	8 (9.9%)
32–43 moderate impact	9 (11.1%)
44–100 severe impact	8 (9.9%)
Median (IQR)	16.00 (IQR 4.0–28.0)
FSFI	
<26.55 sexual dysfunction	42 (51.9%)
≥26.55 sexual wellbeing	39 (48.1%)
Median (IQR)	26.30 (IQR19.4–29.85)
FSDS-R (%), $n=80$[a]	
≤10 no sexual distress	37 (46.35%)
11–14 sexual distress (R)	10 (12.5%)
≥15 sexual distress	33 (41.3%)
Median (IQR)	12.0 (IQR 2.0–22.0)

Abbreviations: DLQI, Dermatology Life Quality Index; FSDS-R, Female Sexual Distress Scale-Revised; FSFI, Female Sexual Function Index; IQR, interquartile range; SKINDEX-29, Health-related quality of life questionnaire with 29 questions.

[a]80 participants filled in the FSDS-R.

significant association with the scores of the DQLI ($P=0.142$), Skindex-29 ($P=0.288$), FSDS-R ($P=0.542$) and FSFI ($P=0.066$). Having had symptoms attributed to VLS in the past year was associated with a significantly poorer score on all four standard questionnaires: DQLI $P<0.001$, Skindex-29 $P<0.001$, FSFI $P=0.004$ and FSDS-R $P=0.006$.

3.4 | Histological features of JVLS

The histological features scored were analyzed for any association with symptoms due to VLS in the past year. Taking our sample size into account, if a feature is present in <10% or >90% of cases, the numbers are too small to study associations with scores on questionnaires or symptoms. Thus, analysis was possible for 13 of the features scored. An association was found between symptoms in the past year and the presence of spongiosis ($P=0.014$), basal apoptotic keratinocytes ($P=0.025$) or high apoptotic cells ($P=0.044$) in the childhood biopsy (Table 5). However, applying the Dunn–Šidák correction for multiple testing of 13 features, these results do not reach statistical significance ($P=0.006$ required). Spongiosis and a high number of apoptotic cells were infrequent (12.2%). Basal apoptotic keratinocytes were seen in 38 (48.1%, about half of the entire study population, $n=80$); in 28 (73.7%) of these cases the respondent reported symptoms within the past year.

3.5 | Open-ended questions

There were 60 respondents (75%) who answered one or more of the open-ended questions. Various recurrent themes are shown in Figure 1. Some women expressed no adverse effect of the VLS on sexuality, whereas others described trepidation about sexual

TABLE 5 Association of histological features in the childhood biopsy with persistence of symptoms (*P*-values ≤0.05 shown in bold[a]).

Histology	Seen in % cases ($n = 80$[b])	Pearson's χ^2	Symptoms past year, *P*
Epidermal atrophy	35.4%	4.517	0.105
Acantosis	39.0%	2.463	0.292
Spongiosis	12.2%	8.525	**0.014**
Lymphocytic exocytosis moderate – profound	31.7%	5.556	0.062
Basal apoptotic keratinocytes	48.1%	11.139	**0.025**
High number of apoptotic cells	12.2%	9.818	**0.044**
Papillary edema	35.4%	0.561	0.755
Melanophages	34.1%	1.967	0.742
Level infiltrate mid-reticular or deeper	41.3%	1.198	0.751
Interstitial infiltrate moderate–profound	84.8%	1.453	0.484
Perivascular infiltrate moderate–profound	66.3%	1.448	0.485
Ectactic vessels	53.7%	2.836	0.586
Hyalinized sclerotic vessels	13.4%	1.574	0.813

[a]Applying the Dunn-Šidák correction for multiple testing of 13 features, the upper limit for significant *P*-values becomes 0.006, so that these results taken together are not statistically significant.

[b]80 participants gave informed consent to evaluate tissue samples; one of these participants did not fill in part 5 of the questionnaire.

encounters and a vulnerability to genital infection or not being able to relax and enjoy sexual encounters for fear of pain or tears. Over half of all respondents elaborated on the negative effect of VLS on their sexual experience or fears of problems with sex later in life. One respondent summed it up as follows, "*I suffer from LS when having sex because I assume in advance that it will be a problem*". Cycling, a daily activity for many in the Netherlands, was noted as a problem. Also, experiencing unknowledgeable professionals was a recurring theme. One woman remarked that "*As a little girl of 7 it was awful to have 5 student-doctors called in to look at my private-parts because I was such an unusual case*". Some women who had not yet become pregnant worried about delivery; however, others who already had given birth, described being counseled and subsequently being able to go through an uncomplicated vaginal delivery.

4 | DISCUSSION

This study analyses the long-term repercussions of JVLS in a cohort of 81 adult females (aged 18–47 years) with histologically confirmed JVLS during childhood or adolescence, median follow-up 19.5 years. An analysis of the effect of disease on QoL and sexuality was carried out. An inventory of their personal and family history as related to VLS was made. Results regarding the obstetric history are also presented. Finally, we looked at any possible relation of current symptoms to the findings in the childhood biopsies. To our knowledge, there are no similar studies of a group of adult women who were diagnosed with JVLS as juveniles, limiting how the results can be brought into perspective with known statistics regarding QoL, sexuality and obstetric outcome.

Both QoL and sexuality were somewhat affected in at least half of the cases. QoL, as scored with the DQLI and Skindex-29, proved favorable in comparison with the literature in which volunteers were recruited from patient associations.[15,16] These differences may reflect the bias of the cited studies, as participants in those studies were members of the Dutch patient association who might more likely have current symptoms and worries. Current symptoms in our study correlate with an effect on QoL and sexuality. The participants in the previous studies were also older, with an average age 50 vs 29.1 in the current study.[15,16,21] Our results concur with the results of van Cranenburgh et al.,[21] who found that a poorer QoL score was associated with less satisfaction with treatment, which could be linked to current symptoms. Owing to the dermatology-specific QoL questionnaires used in the current study rather than a generic questionnaire, the results cannot be compared with the general population.

Compared with the literature, participants in our study scored somewhere between women with VLS and controls for both sexual functioning and sexual distress.[15] Half of the women in the current study scored below 26.55 on the FSFI, indicating low sexual functioning. This is poorer than the aged-matched general Dutch population, where 20% of women 20–30 years women and 17% of women 30–40 years olds reported sexual dysfunction as scored by the FSFI.[22] Respondents expressed their concern about the impact of JVLS on their current or future sexual activity. They also noted that they could not fully reflect their experience with this chronic and remitting disease in the standard questionnaires used. A cardinal aim

FIGURE 1 Some recurrent themes regarding participants' experience with juvenile vulvar lichen sclerosus.

of further research, therefore, should be to find instruments to help gain insight into the experience of these women.

There is limited literature on obstetric outcome with VLS and none specifically addressing JVLS. Previous case reports and smaller series which included up to 36 pregnancies have shown that vaginal delivery is possible in the presence of VLS.[19,23–25] Our series involves 55 deliveries of women with a prior diagnosis of JVLS. When compared with the general Dutch public, the cesarean section rate was similar. There were more high-grade obstetric tears than expected, but with only four cases of OASIS, the numbers remain too small to draw any conclusions and further study is needed.[19,26] A recent publication by Sheffer et al. of a survey with respondents recruited through social media platforms worldwide included 115 pregnancies of which the diagnosis VLS was made prior to the pregnancies and with a mean age at onset of symptoms of 22 years.[27] Presumably, many of these women were diagnosed as juveniles. In that study,[27] the cesarean delivery rate was 33%, similar to the worldwide statistic they cite. In the study by Sheffer et al., OASIS was reported in 12%, double the expected number of 6.3% those authors cite. As discussed, we compared our findings with statistics within the Netherlands (with 17% cesarean deliveries and 2% OASIS) and found similar results, namely cesarean rates were not increased but OASIS was higher. The question arises whether narrowing of the introitus or less flexible skin may have played a role in the cases of OASIS. Interestingly, Sheffer et al. found that symptoms decreased during pregnancy and increased again postpartum, which concurs with previous studies.[19,24,27] The risk of OASIS in the presence of well-controlled VLS as well as the course of disease following a vaginal birth are essential topics that should be addressed.

Despite the current advice that females of any age with VLS should be offered surveillance and maintenance treatment,[5,28] more than half (54%) of the participants were not under surveillance. Autoimmune disease was reported by eight respondents (10%) compared with 3%–5% of the general population[20] and 21.5% of women with VLS at any age.[17] Since auto-immune disease is more likely in the second half of adult life, it is possible that more of the respondents will ultimately develop an auto-immune condition.[29]

At least one-fifth of the participants had not been receiving adequate care, as 20% were not even aware of the childhood diagnosis prior to being recruited for this study. This underscores the need for better counseling of juveniles, given the current advice to continue maintenance and surveillance for symptom control, prevention of scarring and, possibly, prevention of vulva carcinoma later in life.[5,28,30]

Any possible relation of vulva carcinoma specifically to JVLS has yet to be clarified. In our study no respondent had, as yet, developed a vulvar squamous cell carcinoma. However, vulvar squamous cell carcinoma is more likely to occur later in life. It should be noted that Halonen et al.,[31] with national statistics from Finland, found in the youngest group of women with vulvar squamous cell carcinoma aged 30–39 the highest standardized incidence ratio (SIR) of 385 for women previously diagnosed with VLS. Presumably, some of those women had already been diagnosed as juveniles.

Having recent symptoms in adulthood was associated with more apoptotic keratinocytes (both basal and higher in the epidermis) in the childhood biopsy. Correcting for multiple testing, these results do not reach statistical significance. Apoptosis, a marker for cell-death, might indicate more active disease at the moment of biopsy and possibly more continuing damage. These findings illustrate that cellular damage caused by VLS in a juvenile is visible on a microscopic level and may suggest the possibility of ongoing clinical symptoms and permanent repercussions. Findings from studying these biopsies may aid in gaining insight into the pathophysiology of LS. Nevertheless, this is by no means an appeal for biopsy. The diagnosis of JVLS can and should be made by an experienced professional on clinical findings alone.

Strengths of our study include the choice to define a historical cohort based on the histological diagnosis of JVLS regardless of

current disease status and confirmed by expert pathologists. This helped guarantee that, despite the long interval since diagnosis, the inclusions were soundly based on reproducible criteria. The size of the study group and the very long follow-up from time of diagnosis are also strengths. The willingness of the respondents to participate was overwhelming, with 76% of those from the predefined cohort who were traceable taking part, adding strength to the results.

An important limitation of our study is the uncertainty as to how representative this group is for the entire population of females with JVLS, as biopsy is neither a standard nor an advised procedure. Without access to all historical charts, the reasons for the biopsies remain unknown. The charts that could be accessed show that the diagnosis was generally made on clinical grounds, though possibly out of an abundance of caution, because of perceived consequences of the diagnosis for the young patient, the decision was made to confirm the diagnosis with a biopsy. We only reached about half of the potential participants either because the hospital did not participate or because a current address could not be found. Information on clinical evaluation was not available to us, either from the time of original diagnosis or currently. We relied on the recall of the participants, which may have resulted in underreporting of past or current symptoms. Regarding the questionnaires themselves, we did not use any generic questionnaire on QoL, limiting comparison with the general population. Also, the additional questions asked did not go into depth about symptoms, past or present or following childbirth, or other facets of the respondents' experiences with the disease. During further follow-up studies we plan to delve further into these aspects.

As has been shown with other childhood chronic diseases, children often adapt and accept their condition as normal.[32] Therefore, clinical evaluation of the respondents and the current status of the disease is paramount to understanding the long-term consequences of the disease and to what extent maintenance therapy or the lack of it is related to scarring.[28] We are now in the process of personally meeting and clinically assessing participants. The candid answers to the open-ended questions show the need for further study of the themes that were broached. Most participants have expressed an interest in continuing with this ongoing project, as one woman wrote: "*The diagnosis was made when I was a teenager, at an age when you want to go out and discover the world, just like one's peers. The lichen sclerosus always held me back. I hope this research leads to better understanding and guidance for girls with this disease*."

5 | CONCLUSION

This study gives insight into the consequences of JVLS, directly from adults who had been diagnosed many years earlier. The data shed light on the long-term effects of disease on QoL, sexual well-being and persistence of symptoms in adulthood as well as on obstetric outcome. The impact on QoL and sexual well-being in this relatively young study group, as assessed by available instruments, seems to be more favorable then previously reported for VLS but correlates strongly with current symptoms. Over half of the participants had suffered from symptoms within the past year. Though JVLS does not appear to preclude a normal vaginal delivery, the occurrence of more OASIS occurred in the study group than would be expected from population data, illustrates the need for further research on OASIS in the presence of VLS and the course of disease following a vaginal birth. This study lays bare the need for other (types of) LS-specific QOL measures, for an assessment of the obstetric repercussions of JVLS, and for further in-depth study of the challenges facing juveniles and young adults affected by JVLS. This study is hopefully a starting point for further research on this topic, the ultimate goal being to improve care and counseling of these young patients from time of diagnosis onwards.

AUTHOR CONTRIBUTIONS

BM: lead in all of the following: conceptualization, data curation, formal analysis, investigation, methodology, administration, resources, software, validation, visualization, writing original draft and editing paper. IAMvdA: conceptualization, data curation, formal analysis, investigation, methodology, supervision, validation, visualization, writing original draft and editing paper. PCE-G and JD: formal analysis, resources, investigation, methodology, review and editing paper. RS: formal analysis; methodology, validation, visualization, review and editing paper. KNvZ: investigation, project administration, software, review and editing paper. QJM: data curation, investigation, resources, support of administration and review and editing paper. Steering Group members: data gathering and review and editing of the manuscript; MJtK-B and CWB: conceptualization, methodology, supervision, writing original draft and editing paper; SGMAP: conceptualization, methodology, lead supervision, visualization, writing original draft and editing paper.

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CONFLICT OF INTEREST STATEMENT

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

DATA AVAILABILITY STATEMENT

Raw data was generated through the Pathologische-Anatomisch Landelijk Geautomatiseerd Archief (PALGA), Pathology Registry of the Netherlands, queries #LZV2017-148 A1-A9, and at the Erasmus MC University Medical Center, Department of Dermatology and Department of Pathology, repository EMCD19026. The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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APPENDIX A

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