Title: The Vulval Disease Quality of Life Index in women with vulval lichen sclerosus correlates with clinician and symptom scores

Running title: Vulval Disease Quality of Life Index

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Abstract:

Background/Objectives: The Vulval disease Quality of Life Index (VQLI) is a new tool that assesses the burden of vulval disease on quality of life (QoL). Our objective was to assess the correlation between VQLI score and clinician-rated severity scores, overall patient itch/discomfort, disease duration, sexual activity, and age, in vulval lichen sclerosus (VLS) at a vulval disorders clinic.

Methods: A retrospective case note review, including consecutive women with VLS who attended the clinic between April and October 2018. Outcome measures include the VQLI score, clinician-rated severity score, and patient symptom score.

Results: 109 women with VLS were included. On multivariable analysis there was evidence of a positive relationship between VQLI scores and the total clinician-rated score (mean increase in VQLI score per unit increase in clinician score 1.34, 95% confidence interval [CI] 0.31, 2.38; P= 0.01); the relationship was stronger for the cutaneous component. There was little evidence for relationships of the VQLI with the patient’s age, sexual activity, or time since onset of symptoms. There was strong evidence for a positive relationship between VQLI score and overall itch/discomfort score (mean increase 2.38, 95% CI 1.88, 2.88; P <0.001). New and follow-up data were obtained on sequential
visits for 12 women, among whom the VQLI score dropped a mean -2.75 points between visits (95% CI -6.05, 0.55; P = 0.094).

Conclusion: The clinician-rated severity correlates with the impact of VLS on QoL. The VQLI captures information included in a patient itch/discomfort score, which can be easily incorporated into routine assessment.

Key words: Quality of life; vulval lichen sclerosus; outcome measurement; questionnaire; vulval disorders

Introduction:

Quality of life in vulval disease and measurement

Vulval skin disorders can have a significant detrimental effect on a woman's quality of life resulting in anxiety, sexual dysfunction and restriction in daily activities (1).

To date, the impact of vulval disease has been measured with generic tools such as the Hospital Anxiety and Depression Scale (HADS) (2), or with instruments specific to sexual function such as the Female Sexual Dysfunction Scale (FSDS) (3), or vulval pain, for example the Vulval Pain Assessment Questionnaire (VPAQ) (4), sometimes in conjunction with dermatology quality of life scales.

A new patient reported outcome measure (PROM) has been developed that is specific for vulval disorders, namely the Vulval disease Quality of Life Index (VQLI). The VQLI assesses the impact of vulval disease with regard to physical symptoms, activities and functions, relationships, and psychosocial impact. The instrument has been validated and found to be reliable (5).

Lichen sclerosus
Lichen sclerosus is a chronic inflammatory dermatosis that mainly affects anogenital skin. The prevalence of vulval lichen sclerosus (VLS) is estimated to be 1.7 - 3% (6, 7). It most commonly occurs in perimenopausal and postmenopausal women (8). The exact prevalence is unknown and likely underestimated due to misdiagnosis (7), or women failing to present due to self-management, often for candida, or embarrassment (8).

The aetiology of lichen sclerosus is also unknown. Autoimmune mechanisms and genetic factors may be involved in the pathogenesis (9, 10).

The most common symptom of VLS is itch, but pain, dyspareunia, and dysuria may also occur secondary to erosions, fissures, or architectural changes caused by postinflammatory scarring (8, 11). In addition women with VLS are at an increased risk of developing squamous cell cancer of the vulva, possibly up to more than 300 times higher than for women of the same age without lichen sclerosus (12).

There is no cure for lichen sclerosus, but treatment can effectively relieve symptoms, prevent further anatomic changes, and possibly reduce risk of malignancy (13, 14). The 2018 British Association of Dermatologists guidelines for treatment of women with lichen sclerosus include the use of super potent topical corticosteroids, such as clobetasol propionate 0.05% ointment, following a standard regime of daily applications for one month, tapering to a 2-3 times weekly application according to symptom control, for at least 3 months. Treatment is titrated to control symptoms, and to resolve skin thickening and ecchymosis (11).

Treatment outcomes are currently measured by physician rated global clinical severity, including skin and architectural changes, and patient reported symptom relief. There is however a broader impact of VLS on quality of life, which is not systematically measured.

Aims
The aims were to assess the correlation between the VQLI score and objective clinician rated severity scores, patient rated symptom scores, age, sexual activity, and time since onset of symptoms, and to assess change in score with treatment.

Methods

This retrospective case note review was undertaken at a single tertiary referral vulval clinic. Ethics approval was obtained from the Royal Women’s Hospital Human Research Ethics Committee.

Participants

Participants comprised all women (new or review) who attended the vulval disorders clinic between April and October 2018 with either a clinical or biopsy-proven diagnosis of VLS. The clinical diagnosis was confirmed by a dermatologist who specialises in vulval disorders.

The Vulval Quality of Index (VQLI) questionnaire was introduced to the vulval dermatology clinic in 2018. Patients attending the clinic routinely completed this questionnaire upon arrival.

There was no change to usual care or follow-up schedule for these women.

Questionnaires

The VQLI (appendix A) includes 15 questions addressing the impact of vulval disease on the patient over the previous one week. It covers physical symptoms, activities and functions, relationships, and psychosocial impact. Similar to the Dermatology Life Quality Index (15), each question is scored from 0 to 3 corresponding to responses: “not at all”, “a little”, “a lot” or “very much”. The maximum score is 45. Higher scores indicate greater impairment of quality of life. The total VQLI score was calculated and recorded. Sub scores of separate
domains (such as symptoms, relationships, future health concerns) were not recorded.

The version of the VQLI used in this study was the most recent available as of April 2018 (5). It is not the final version. At the time of writing this article, the questionnaire has been developed further by its original authors but has not yet been published (Personal communication).

Data collection

At each patient’s visit we recorded the VQLI score, the global clinician rated severity score, the patient’s reported global symptom score, disease duration according to onset of symptoms, and age.

The global clinician rated severity score comprised assessment of architectural and cutaneous changes. Architectural and cutaneous scores were each scored on a scale of 0-3, 0 representing normal skin or architecture and 3 representing severe skin or architectural changes. The sum of these two scores produced the total clinician rated severity score, on a scale of 0-6. The degree of severity was assessed at each visit by a dermatologist.

The patient’s global symptom score referred to the overall itch/discomfort experienced in the previous one week, and was measured using a numeric rating scale of 0-10.

Women completed the VQLI questionnaire at the beginning of their clinic appointment, with the assistance of interpreters if required.

Scores and demographic data were collected from clinical records, de-identified and entered into a Microsoft Excel database.

Statistical analysis
Data were analysed using Microsoft Excel 2016, SPSS version 24 and Stata version 15. Relationships between continuous variables were determined by linear regression models fitted using generalized estimating equations fitted and reported with robust (sandwich) estimates of standard errors to account for more than one observation in some participants. Regression coefficients and their 95% confidence intervals (CIs) were obtained from the regression models.

Major interest was in the relationships between the VQLI and the clinician scores. Covariates of age, duration since the onset of symptoms, and being sexually active were added to the models to determine their relationships to the VQLI and to adjust for any effect on the main relationship between the VQLI and the clinician ratings. We also determined the relationships of the VQLI with the patients’ itch/discomfort scores, and whether the patients were new to the clinic or returning for review.

Paired t-tests were used to compare the VQLI before and after treatment within the same participant, where such data were available. P values <0.05 were considered statistically significant.

Results

Data were available for 109 women during the study period; not all participants had complete data for all items. The response rate was known precisely for 21 of the total 23 clinics. For 11 of the 21 clinics, 91.4% of women attending with VLS completed questionnaires. For 10 of the clinics, 69.0% completed questionnaires. Data on the inclusion rate were missing for two clinics. A weighted average calculation, with 69% as the presumed proportion for the 2 of the 23 clinics, was used to estimate an overall response rate of 80%.

The 109 women were aged 23 to 91 years with a median age of 61 years (Table 1). Thirty patients (28%) were new to the clinic. Thirty-two of 91 (35%) patients who responded to the question were sexually active. Duration since the onset of symptoms ranged from under one month to 37 years (mean 6.7 years) (Table 1).
The mean time since onset of symptoms for patients new to the clinic was 4.6 years, whereas it was 7.9 years for previous clinic patients (mean difference -3.3 years, 95% CI -6.2, -0.4; P=0.025). The median for the total clinician rated score was 3 (out of 6), for the VQLI was 12 (out of 45), and for the itch/discomfort score was 5 (out of 10) (Table 1).

On both univariable and multivariable analyses there was little evidence for relationships between the VQLI and the patient's age, duration of symptoms, or being sexually active (Table 2). On univariable analysis there was weak evidence for a positive relationship between the VQLI score and the global clinician rated severity score (mean increase in VQLI score per unit increase in clinician score 1.01, 95% CI -0.07, 2.08, P = 0.07); the strength of the evidence increased on multivariable analysis (mean increase in VQLI score per unit increase in clinician score 1.34, 95% CI 0.31, 2.38, P = 0.01). On multivariable analysis the evidence was stronger for a relationship between the VQLI and the cutaneous component of the clinician score (mean increase in VQLI score per unit increase in cutaneous clinician score 2.09, 95% CI 0.23, 3.95, P = 0.028) than for the architectural component (mean increase in VQLI score per unit increase in architectural clinician score 1.18, 95% CI -0.59, 2.95, P = 0.19).

There was strong evidence for a linear relationship between the VQLI score and the overall itch/discomfort score (mean increase in VLQI score per unit increase in itch/discomfort score 2.38, 95% CI 1.88, 2.88, p <0.001) (Figure 1).

Data were obtained on two sequential visits in 12 women. Among these patients the VQLI score dropped a mean -2.75 points between the initial and follow up visit (95% CI -6.05, 0.55, P = 0.094), with the total clinician score decreasing by a mean of -0.33 (95% CI -1.20, 0.54, p = 0.42).

There was little evidence for a difference in the VQLI score between those new to the clinic or those attending for review (mean difference -2.88, 95% CI -7.06, 1.30), P = 0.18).
Treatments instituted at clinic are listed in table 3.

Discussion

In conditions where there is a significant impact on quality of life, the use of PROMs is essential, both for therapeutic decision making, and to standardise outcome measures for therapeutic trials.

Women with VLS experience significant sexual dysfunction and distress (16, 17), as well as somatic symptoms and emotional distress (18), with a significant overall impact on health related quality of life (19, 20). However, this impact is infrequently measured in routine clinical practice as demonstrated by Simpson et al (21). In the clinical trial setting, there is heterogeneity of patient reported outcomes and instruments used to measure these. This is summarised in a systematic review of 28 randomised controlled trials investigating therapeutic interventions in vulval disease, illustrating the use of 25 different outcomes and 49 separate outcome measurement instruments (22), few of which have been validated for use in vulval disease. There is a pressing need for a standardised core outcome set in vulval disorders and validated measurement instruments in order to improve research and treatment outcomes for women with vulval disease (23).

The VQLI is a newly validated PROM which we have implemented into standard assessment in clinical practice. The results of this study indicate that the clinician-rated severity score, and in particular the cutaneous component of the score, correlates with the VQLI score. The cutaneous appearance of VLS is indicative of active inflammation. A high cutaneous severity score would likely reflect high somatic scores of itch and pain/discomfort, and understandably significant QoL impacts. In contrast, severe architectural changes could be present in inactive, well-controlled VLS. The cutaneous scores, as opposed to architectural scores, can be more easily improved with topical ointments.
There was a weaker correlation between the VQLI score and the architectural component of the clinician-rated severity score. It is possible that a stronger correlation might be found in sub-domain analysis of the VQLI. Architectural changes, including narrowing of the introitus and resorption of the clitoral hood, might correlate more significantly with subdomains including feelings and relationships/sex.

The VQLI score was found to correlate strongly with the overall patient symptom score (itch or discomfort) on a numeric rating scale. This finding is consistent with that of van de Nieuwenhof et al (16) that patients who experienced more vulval itch or pain reported greater sexual distress. This overall symptom score therefore partially summarises the information captured by the VQLI.

The small cohort of patients with two visits within the study time frame, demonstrated a marginal improvement in VQLI (mean drop of 2.75 points) and total clinician score (mean drop of 0.33 points). Other studies have found that patients with VLS were at least moderately satisfied with standard treatment (18, 20, 24).

An Australian study of 507 women with VLS treated with topical corticosteroids found that suppression of symptoms occurred in 93.3% of compliant patients, and only 58.0% of partially compliant patients (p < 0.001) (25). Their treatment regime involved daily application of a potent topical corticosteroid until follow up (i.e. for at least 3 months), followed by gradual weaning to long-term preventative management according to symptom and disease control. The desired outcome was symptom resolution and normal skin appearance and texture. The treatment regime used in our study followed the BAD guidelines (11), which involved the application of a super potent topical steroid used daily for 1 month, then on alternate days for 1 month, and then twice weekly, rather than the more tailored approach of Lee et al. In our study, compliance was not measured. Only 12 patients had data for sequential visits for whom there was only a 2.75 drop in VQLI score, maybe this reflects the treatment regime used, or possibly the inclusion of poorly compliant patients.
We were unable to analyse the different domains of the VQLI questionnaire individually, because only total VQLI scores were recorded. While we have seen an overall trend towards improvement in VQLI scores in women who have had sequential clinic visits, we cannot determine whether all domains improved, or whether just somatic symptoms and related functional components improved after treatment of the active VLS.

No correlation was seen between patients’ age and the total VQLI score, indicating the high impact across all age groups. It is possible that age related differences exist between domains of the questionnaire, for example sexual function, and emotional and somatic impact. A more detailed sub scoring system may be required to fully address different concerns across age groups.

No correlation was seen between the VQLI score and whether the patient was new or attending for review. This may reflect the management strategy, poor compliance, or more regular review of those with more severe disease.

No correlation was seen between the VQLI score and the onset of patients’ symptoms which was used as a proxy for disease duration. A possible explanation is inaccurate recall of onset of mild symptoms. Early diagnosis and adequate treatment is key to prevent complications of VLS. Studies have shown that a longer diagnostic delay correlates to a lower quality of life (19, 26), which was not evident in our findings. The average length of symptoms prior to their first appointment was 6.7 years, indicating ongoing problems with a delay in diagnosis and intervention for women with VLS.

Limitations of this study include its retrospective nature, however all the data were collected and documented prospectively, thus reducing the risk of information error and bias. In addition, the clinician rated score is not validated, however it provided a more objective assessment than summarising clinicians’ descriptive terms, such as mild or severe. Selection bias is possible given that approximately 20% of women failed to complete the questionnaire and are
therefore not included in the analysis. However, an 80% response rate is likely to have been representative of the overall population attending. A further limitation is the small cohort of patients with sequential data and as such we are unable to comment on the sensitivity of the VQLI to change with treatment. Finally, the study was undertaken at a tertiary referral vulval disorders clinic, therefore the results may not be readily generalisable outside this population.

Strengths include the high proportion of women included in the study with complete data; the prospective nature of data entry; the attempt to standardise clinician assessment with a scoring system; and the availability of interpreter services to help with the questionnaire to maximise inclusion.

To date there has been no validated tool specific for vulval disease. As such, the VQLI offers a new opportunity in clinical assessment for routine practice and clinical trials. This study has highlighted the usefulness of including a numerical rating scale of patient reported symptoms (itch/discomfort) in routine assessment, as this correlated significantly with the total VQLI score. The VQLI score also correlated with the clinician rated severity score, and in particular the cutaneous component, which is indicative of active inflammation. Our study has also highlighted the need to include sub-domain analysis in order to tailor treatment according to the patient’s individual need, whether that is addressing anxiety, relationships and sexual function, future health concerns or other functional impact.

Further research is required regarding what constitutes a clinically significant change in the VQLI score as well as its responsiveness to change with treatment.

References


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Figures legend:
Figure 1: VQLI score correlation with patient rated overall itch/discomfort score

Tables:

Table 1: Ranges, means, and medians for patient age, duration of symptoms, and outcome measures including VQLI score and clinician rated severity score for 109 participants

<table>
<thead>
<tr>
<th></th>
<th>Range</th>
<th>Mean (SD)</th>
<th>Median (25&lt;sup&gt;th&lt;/sup&gt;–75&lt;sup&gt;th&lt;/sup&gt; centiles)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>23 - 91</td>
<td>60.3 (14.9)</td>
<td>61 (50, 70)</td>
</tr>
<tr>
<td>Duration of symptoms</td>
<td>0 - 37</td>
<td>6.7 (7.0)</td>
<td>6 (2, 10)</td>
</tr>
<tr>
<td>before clinic review</td>
<td>(years) n=103</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VQLI score n=103</td>
<td>0 – 45</td>
<td>14.6 (10.5)</td>
<td>12 (6, 22)</td>
</tr>
<tr>
<td>Total clinician rated</td>
<td>0 – 6</td>
<td>2.7 (1.5)</td>
<td>3 (2, 3.9)</td>
</tr>
<tr>
<td>severity score n=100</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Univariable and multivariable associations with VQLI

<table>
<thead>
<tr>
<th></th>
<th>Univariable</th>
<th>Multivariable</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean difference* (95% CI) n</td>
<td>P- value</td>
</tr>
<tr>
<td>Age (years)</td>
<td>-0.05 (-0.16, 0.07)</td>
<td>0.41</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Duration of symptoms before clinic review (years)</th>
<th>n=121</th>
<th>n=85</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-0.10 (-0.38, 0.17)</td>
<td>0.44 (-0.41, 0.22)</td>
</tr>
<tr>
<td>Sexually active</td>
<td>n=108</td>
<td>n=85</td>
</tr>
<tr>
<td></td>
<td>2.3 (-1.7, 6.4) n=99</td>
<td>2.6 (-2.5, 8.8) n=85</td>
</tr>
<tr>
<td>Total clinician rated severity score</td>
<td>n=106</td>
<td>n=85</td>
</tr>
<tr>
<td></td>
<td>1.01 (-0.07, 2.08)</td>
<td>0.07 (0.31, 2.38)</td>
</tr>
</tbody>
</table>

*change in VQLI score per unit change in independent variable

Table 3: VLS treatments instituted at the vulval clinic

<table>
<thead>
<tr>
<th>Topical treatment</th>
<th>Number of patients (percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=109</td>
<td></td>
</tr>
<tr>
<td>Clobetasol propionate 0.05% ointment blitz (daily) (superpotent topical steroid)</td>
<td>37 (34)</td>
</tr>
<tr>
<td>Clobetasol propionate 0.05% ointment twice weekly (superpotent topical steroid)</td>
<td>14 (13)</td>
</tr>
<tr>
<td>Betamethasone dipropionate 0.05% ointment (potent topical steroid)</td>
<td>31 (28)</td>
</tr>
<tr>
<td>Methylprednisolone aceponate 0.1% fatty ointment (moderate potency topical steroid)</td>
<td>15 (14)</td>
</tr>
<tr>
<td>Other (e.g. tacrolimus 0.1% ointment, or no therapy)</td>
<td>12 (11)</td>
</tr>
</tbody>
</table>
Appendix A: The Vulval Disease Quality of Life Index (VQLI) questionnaire

**TREATMENT**

1. Over the past month, how much of a problem has the treatment of your vulval symptoms been (for instance messy creams, time consuming, expensive, inconvenient)?
   - Very much □
   - A lot □
   - A Little □
   - Not at all □

**SYMPTOMS**

2. Over the past month how itchy, painful, stinging and/or burning has your vulval skin felt?
   - Very much □
   - A lot □
   - A Little □
   - Not at all □

3. Over the past month, how often have you felt any of the following symptoms; pain when urinating, painful intercourse, heat intolerance, discharge or wetness?
   - Very much □
   - A lot □
   - A Little □
   - Not at all □
FEELINGS

4. Over the last month how embarrassed or self-conscious have you been because of your vulval symptoms?
   - Very much □
   - A lot □
   - A Little □
   - Not at all □

5. Over the past month how much has your vulval skin impacted your body image or sense of self? (for instance your femininity, feeling isolated, feeling different)?
   - Very much □
   - A lot □
   - A Little □
   - Not at all □

6. Overall how distressed or anxious have you felt because of your vulval skin over the last month?
   - Very much □
   - A lot □
   - A Little □
   - Not at all □

ACTIVITIES

7. Over the last month how much has your vulval skin influenced your choice of clothing (underwear, jeans)
   - Very much □
   - A lot □
   - A Little □
   - Not at all □

8. Over the last month how much has your vulval skin disturbed your sleep?
9. Over the last month how much has your vulval skin made it difficult for you to go shopping, look after yourself or your family, home and garden?

Very much □
A lot □
A Little □
Not at all □

10. Over the last month how much has your vulval skin made it difficult for you to attend social or leisure engagements? (for instance going out for dinner, or bars, dating, exercise class, gym)

Very much □
A lot □
A Little □
Not at all □

11. Over the last month how much has your vulval skin interfered with your ability to concentrate on work or study?

Very much □
A lot □
A Little □
Not at all □

RELOCATIONS/ SEX

12. Over the last month how much has your vulval skin created problems with a partner or precluded you from pursuing a romantic relationship? (for instance maintaining a relationship or finding a partner)

Very much □
A lot □
13. Over the last month how much has your vulval skin interfered with your sex life? (Including: decreased libido, decreased frequency of sex and/or enjoyment of sex)
   - Very much □
   - A lot □
   - A Little □
   - Not at all □

14. Over the last month how often have you felt distressed or worried about sex because of your vulval skin?
   - Very much □
   - A lot □
   - A Little □
   - Not at all □

**FUTURE HEALTH CONCERNS**
15. How often in the last month have you been worried about long-term health implications of your vulval skin condition? (for instance concern about developing cancer or difficulties with fertility)
   - Very much □
   - A lot □
   - A Little □
   - Not at all □

**Scoring Key:**
- Very much = 3; A lot = 2; A little = 1; Not at all = 0
- Total Score: ____/45
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