

RESEARCH REPORT

Prospective study of patch testing in patients with vulval pruritus

Emma Haverhoek, Catherine Reid, Lynne Gordon, Gillian Marshman, Jane Wood and Priya Selva-Nayagam

Flinders Medical Centre and Royal Adelaide Hospital, Adelaide, South Australia, Australia

SUMMARY

Forty-three patients with the primary complaint of vulval pruritus were recruited to take part in this prospective patch-testing study. A detailed questionnaire was administered to each and patch testing to an extended battery of allergens was undertaken. This included the European standard series, preservatives, corticosteroids and a battery of common over-the-counter topical vulval treatments. Analysis of demographic data and prior treatments used, and various other parameters, were studied in the context of patch-test results. This prospective study reports a very high rate of contact sensitivity in patients presenting with vulval pruritus, with 81.4% of those tested having at least one contact allergen detected. One or more clinically relevant allergens were found in 44% of the subjects patch tested. The variables found to predict a greater likelihood of a contact allergy were a biopsy diagnosis of vulval dermatitis, the use of multiple topical treatments, sexual inactivity and patients with severe pruritus on a self-reported scale. Most importantly, many clinically relevant allergens these patients reacted to were outside the European standard series. This highlights the need for an extended series in this patient population.

Key words: atopy, fragrance, lichen sclerosus, nickel, preservatives.

INTRODUCTION

Vulval pruritus may be attributable to a primary vulval dermatosis, but allergic contact sensitivity may often occur as a secondary phenomenon.¹ The likelihood of this increases with the use of multiple prescribed and over-the-counter remedies to alleviate the symptoms.^{1,2}

The role of patch testing in patients presenting with vulval pruritus has been evaluated in the past. However, the majority of such studies were retrospective case note reviews.^{1,2} In addition, one prospective study that was undertaken selected patients in whom 'a contact element was considered at least possible'.⁵ In this study, a selection bias is stated and this is also likely in the retrospective studies. That is, patients with a higher suspicion of contact allergy are more likely to be patch tested than the other patients attending the clinics. Therefore, this may influence the final results.

The aim of the current study was to affirm with a prospective study that allergic contact sensitivity is common in patients presenting with vulval pruritus, using detailed demographic and clinical data.

METHODS

Human ethics committee approval was sought and obtained from three major teaching hospitals. The study was advertised via a letter to all dermatologists and gynaecologists in the Adelaide metropolitan area, requesting referral of patients with the primary symptom of vulval pruritus. Once referred, the consent of each patient was obtained and they completed a detailed questionnaire prior to being clinically assessed by a dermatologist. The patients underwent patch testing to an extended series of allergens, comprising the European standard series, preservatives, corticosteroid series and a series of commonly used topical vulval medicaments (Table 1). The majority of the European standard, preservative and corticosteroid allergens were

Correspondence: Dr Emma Haverhoek (nee Storer), Department of Dermatology, Royal Adelaide Hospital, North Terrace, Adelaide, SA 5000, Australia. Email: e_storer@hotmail.com

Emma Haverhoek, MB BS. Catherine Reid, FACD. Lynne Gordon, FACD. Gillian Marshman, FACD. Jane Wood, FRANZCOG. Priya Selva-Nayagam, FACD.

The preliminary results of this study were presented at The Australasian College of Dermatologists' 40th Annual Scientific Meeting, Adelaide, Australia, 13–16 May 2007.

Submitted 24 September 2007; accepted 22 January 2008.

Abbreviation:

RAST

radioallergosorbent test

Table 1 Patch tests applied

Standard series	Preservatives
Potassium dichromate 0.5%	Chlorocresol 1%
Neomycin sulphate 20%	Chloroxylenol 1%
Thiuram mix 1%	Bronopol 0.5%
Paraphenylenediamine 1%	Imidazolidinyl urea 2%
Cobalt chloride 1%	Phenylmercuric acetate 0.01%
Benzocaine 5%	Sorbic acid 2%
Formaldehyde 1%	Chlorhexidine digluconate 0.5%
Colophony 20%	Chloracetamide 0.2%
Clioquinol 5%	Glutardialdehyde 0.3%
Balsam of Peru 25%	Thiomersal 0.1%
4-Phenylenediamine base 0.1%	Chlorquinaldol 5%
Wool alcohols 30%	Benzalkonium chloride 0.1%
Mercapto mix 1%	Triclosan 2%
Epoxy resin 1%	Diazolidinyl urea 2%
Paraben mix 16%	Butyl hydroxytoluene 2%
PTBP-resin 1%	Butyl hydroxyanisole 2%
Fragrance mix 8%	Dodecyl (lauryl) gallate 0.3%
Quaternium-15 1%	Tert-butylhydroquinone 1%
Nickel sulphate 5%	Propyl gallate 0.5%
Kathon 0.01%	Octyl gallate 0.5%
Mercaptobenzthiazole 1%	
Sesquiterpene lactone mix 0.1%	
Primin 0.01%	
Corticosteroid series	Miscellaneous
Amcinonide 0.1%	Disperse blue
Betamethasone-17-valerate 0.12%	Basic red 46
Clobetasol-17-propionate 0.25%	Gold thiosulphate
Hydrocortisone 1%	
Hydrocortisone-17-butyrate 0.1%	Vulval treatments
Triamcinolone acetonide 0.1%	Paraderm plus®
Budesonide 0.1%	Pevaryl® cream
Prednisolone 1%	Vagisil® cream
	Ovestin® cream
	Resolve® cream
	Canesten® cream
	Lavender oil
	Nilstat® cream
	Hydraderm® cream
	Tea tree oil

manufactured by Chemotechnique® and were in petrolatum. The author-designed series of vulval medicaments were used neat (Table 2).

The patients attended first at day 1 for application of the allergens in Finn chambers, fastened with Hypafix® (Smith and Nephew) and Micropore® (3M Health Care Ltd) then attended on day 3 for the allergens to be removed and the initial reading. They returned on day 5 for the final assessment, as per standard patch-testing practice.⁴ For '+' reactions and greater at day 5, patients were provided with detailed information regarding the chemical they reacted to, and where this may be encountered in their everyday living. The patients were advised to avoid substances containing the allergens to which they had reacted.

The results were summarized in a spreadsheet and the number of contact allergens each patient reacted to was calculated. The patients were grouped based on the following variables: histological diagnosis, atopic or not, two or more past allergies (self-reported) versus none, the use of a

Table 2 Topical vulval medicaments patch tested and their ingredients

Product and manufacturer	List of ingredients
Vagisil® (Combe International)	Benzocaine, resorcinol, methylhydroxybenzoate, sodium sulfite anhydrous
Paraderm plus® (Wyeth Healthcare)	Chlorhexidine gluconate, lignocaine hydrochloride, bufexamac
Pevaryl® (ICN Pharm.)	Econazole, benzoic acid
Ovestin® (Organon Inc.)	Chlorhexidine hydrochloride, octyldodecanol, cetyl alcohol, cetyl esters wax, glycerol, stearyl alcohol, polysorbate 60, sorbitan monostearate, lactic acid, sodium hydroxide
Resolve® (Ego Pharm.)	Miconazole, phenethyl alcohol
Canesten® (Bayer)	Clotrimazole, benzyl alcohol, sorbitan stearate, polysorbate 60, cetyl palmitate, cetostearyl alcohol, octyldodecanol, purified water
Lavender oil (In Essence®)	<i>Lavandula angustifolia</i>
Nilstat® (Sigma Pharm.)	Nystatin, isopropyl myristate, sorbic acid, wax emulsifying, glycerol, purified water, sodium hydroxide
Hydraderm® cream (Sigma Pharm)	Chlorocresol, cetamacroglol, propylene glycol, cetostearyl alcohol, liquid and white soft paraffin, sorbolene, purified water.
Tea tree oil (Thursday Plantation)	Melaleuca oil

greater or lesser number of topical vulval treatments, as well as those with a duration of symptoms greater than 5 years versus those with duration less than 1 year. In addition, sexual activity, use of condoms, pubic hair removal methods and severity of symptoms were addressed. For each variable, the average number of contact allergens for each group was calculated and compared.

In addition, most of the patients were reviewed subsequently by one of the authors to ascertain the clinical relevance of contact allergens. The allergen was deemed relevant when it had been used directly on the vulval area and clinical improvement was documented by the assessing dermatologist following avoidance of this treatment.

RESULTS

A total of 43 patients was recruited and patch tested, with a mean age of 42 years. Their ages ranged from 20 to 80 years, with 28 of the 43 being premenopausal. The majority of referrals were from dermatologists (79%). Thirty-two of the patients were followed up after 6–12 weeks.

Of the 43 patients, 35 (81.4%) reacted to one or more allergens. Eleven of 43 (26%) had one reaction only and 11 of 43 reacted to four or more allergens. A total of 19 patients

Table 3 Histological diagnosis and patch-test results

Biopsy	Average no. of allergens	Common positive tests
Dermatitis (23 patients)	2.7 (range 0–12)	Relevant: Vagisil® Other: nickel, cobalt, tea tree oil
Lichen sclerosus (5 patients)	0.8 (range 0–5)	One relevant allergen: Vagisil®
Plasma cell vulvitis (1 patient)	10 allergens, 5 relevant.	Relevant allergens: clioquinol, Vagisil®, benzalkonium chloride.
Psoriasis (1 patient)	Nil	Nil

Table 4 Atopy and patch-test results

Atopic	No. of patients	Positive patch-test rate	Common positive tests
Yes	31	87% Average 2.8 allergens (range 0–12)	Nickel, cobalt chloride, fragrance mix [†] , Vagisil® [†]
No	12	75% Average 1.75 allergens (range 0–5)	Tea tree oil, Vagisil® [†] , nickel.

[†]Relevant allergens for vulval pruritus.

(44%) were shown to have at least one clinically relevant allergen, by virtue of improvement of their vulval pruritus after avoiding the use of the substance. Four subjects who had reacted to allergens during their patch testing were lost to follow up.

A total of 31 (72.1%) of the 43 patients had a histological diagnosis prior to patch testing; the results are shown in Table 3 in the context of their patch-test results. Vagisil® is a clinically relevant allergen in most categories. It is a common over-the-counter vulval pruritus remedy and a list of ingredients can be found in Table 2.

Of the 23 patients with a biopsy diagnosis of dermatitis, 48% of those had clinical relevance of one or more detected allergens at follow up.

Of the 43 patients, 31 reported a past and/or present history of asthma, eczema and/or hayfever. Therefore, the atopic rate in this study was 69%. The patch-test results of the atopic versus the non-atopic patients are summarized in Table 4. Thirteen of the 31 (42%) atopic patients were deemed to have one or more clinically relevant allergens versus six of the 12 (50%) non-atopic patients.

Of the 31 patients who declared a past or current history of asthma, eczema and/or hayfever (the 'atopic' group), 19 of those patients (61%) had a biopsy diagnosis of vulval dermatitis. These patients had the same rate of positive reactions as the rest of the patients in the atopic group in our study.

The previous allergies of the patients were self-reported in the questionnaire and were grouped as follows: medications, cosmetics/creams, jewellery/metals, tapes/adhesives and other. 'Multiple allergies' was defined as patients who reported allergies from two or more of the categories listed above. Eleven of the 43 patients reported multiple past allergies, and seven of those 11 reacted to more than three allergens each: the majority of these allergens being preservatives. Five of the 11 (45%) patients with multiple past allergies had clinically relevant contact allergens identified.

Of the eight patients who reported an allergy to metals, six reacted to nickel sulphate and/or cobalt chloride. Those

Table 5 Severity of pruritus and patch-test results

Symptoms	Average no. of allergens	Patients with clinically relevant allergens (%)
Severe (4 or 5 out of 5) 15 patients	2.5 allergens (range 1–12)	60
Mild (1 or 2 out of 5) 7 patients	1.4 allergens (range 0–3)	28

patients who reported an allergy to cosmetics all reacted to either fragrance and/or preservatives.

There were 16 patients in the study who had vulval symptoms for 5 years or longer (37%). The longest duration of vulval pruritus was 30 years. Patients with symptoms of more than 5 years on average reacted to the same number of allergens as those who had had vulval pruritus for 1 year or less. That is, in this study duration of symptoms did not correlate with contact sensitization.

The objective severity of vulval pruritus was recorded as part of the baseline questionnaire. The results of this are summarized in Table 5, showing that patients with the more severe pruritus on our self-reported scale had a greater likelihood of relevant contact allergy compared with those who reported less severe symptoms.

In this study, 28 of 43 patients (65%) of patients reported having a rash associated with their primary complaint of vulval pruritus. Fifteen of 43 (35%) reported the combination of rash and burning. Other symptoms reported included pain and discharge, although rash and burning sensation were the most common associated complaints.

Table 6 summarizes the patch-test results with respect to sexual activity.

None of the patients who used condoms reacted to the rubber allergens in the European standard series. In this study, RAST to latex was not performed.

Patients were questioned regarding their preferred methods of pubic hair removal, if any. Thirty of 43 (70%)

Table 6 Sexual activity and patch-test results

Sexually active	No. of patients	Average no. of allergens	Patients with clinically relevant allergens (%)
Yes	26	2.3 (range 0–10)	35
No	17	2.9 (range 0–12)	59

Table 7 Number of topical treatments used and patch-test results

No. of topical treatments (categories)	No. of patients	Patients with clinically relevant allergens (%)
4 or more	21	57
1–2	6	17

did not undertake pubic hair removal at all. Seven of the patients waxed and the remaining six used shaving. Using the various hair removal methods did not predict a greater likelihood of contact sensitivity, and potentially relevant allergens, such as nickel for those who shaved, were no more prominent than for those who did not undertake hair removal at all.

The patients were asked to summarise what topical treatments they had used for their vulval pruritus. These were listed in the following six categories: corticosteroid creams/ointments, antifungal/antiyeast creams, anti-itch creams (e.g. Vagisil®), moisturisers/cleansers, oestrogen/hormonal creams and other.

The patch-test results of those patients who reported use of a greater number of topical products (four or more treatment categories) compared with those who used the least (one or two treatment categories), are summarized in Table 7. Seven of these 21 patients reacted to medicaments from the 'vulval treatments' series, including five who reacted to tea tree oil and three who reacted to Vagisil®. All of the patients who reacted to Vagisil® had used it before and improved with cessation of use. Tea tree oil was not reported by the patients as being used directly on the vulva to alleviate pruritus, although it is now contained in numerous topical preparations used elsewhere on the body. It was not a clinically relevant allergen in this setting.

The vast majority of patients (95%) used topical corticosteroids at some time to treat their symptoms, but only two reacted to any allergens in the corticosteroid series. Only one of these was deemed clinically relevant on follow up, as the other patient failed to attend for later assessment.

DISCUSSION

In previous studies, allergic contact sensitivity has been shown to be a factor in perpetuating symptoms of those suffering vulval pruritus.^{1–3} The first published data involved a retrospective study of 135 patients with persistent vulval symptoms.² Their patch-test results were reviewed and it was found that contact sensitivity was common among these patients, with a total of 47% of those tested having positive reactions.² The most common allergens were medicaments,

including neomycin, clobetasol and ethylenediamine.² Another retrospective study documented patch-test results for patients with 'primary pruritus vulvae'.¹ That study used an extended battery and found that 49% of patients with 'pruritus vulvae' had at least one relevant contact allergen detected. The most frequently identified allergen was a medicament called Lanacane® (Combe International), which is an over-the-counter anti-itch remedy sold in the UK. It contains benzocaine, triethanolamine and fragrance, and appears to be a product similar to Vagisil®, a common positive in the current study.

A prospective patch-test study has been performed, but which focused particularly on those with a history suggestive of vulval contact dermatitis. That study compared patch-test results with the prior clinical or histological diagnosis and used an extended battery including standard series, medicaments, preservatives and corticosteroids. Nickel was the most common allergen in that series of patients, followed by fragrance mix and medicaments.⁵

Nickel and cobalt chloride were common allergens in this study, replicating prior patch-test results in patients with vulval pruritus. However, the clinical relevance of this has been debated.^{2,5} One study thus far has supported the relevance of these allergens in the clinical setting by demonstrating an improvement of vulval pruritus with dietary nickel avoidance.⁵

In this study, the majority of patients had a histological diagnosis prior to patch testing. The variety of dermatoses detected by biopsy reflected the most common disorders found in previous studies of symptomatic vulval disease.^{6–8} The majority of patients had a biopsy diagnosis of dermatitis prior to patch testing, and these patients had a high rate of contact sensitivity. Other studies have focused on clinical diagnoses and have reported a similar rate of relevant positive patch tests in the patients with dermatitis as opposed to other dermatoses.^{2,9–11} Comparisons between patients with vulval dermatoses besides dermatitis were difficult in this study due to small numbers.

A previous study reported seven patients with plasma cell vulvitis, only one of whom had a positive patch-test reaction.¹² Plasma cell vulvitis is not generally associated with pruritus; however, the patient who did have positive patch-test results in that study suffered vulval itch. Our study only had one patient with a histological diagnosis of plasma cell vulvitis. However, she reacted to multiple allergens on patch testing. This particular patient also experienced burning and pruritus in the setting of plasma cell vulvitis, which is usually asymptomatic. The presence of pruritus may indicate patients with this condition who have developed secondary allergic contact vulvitis.

Prior studies of contact sensitivity in patients with vulval pruritus have not clarified the true incidence of atopy in their patient population.^{3,11,15} In a previous vulval pruritus patch-test study, a past history of eczema was reported in 16 of 50 patients, but asthma and hayfever were not taken into account.⁵ In that study, eczema did not correlate with contact allergy. In the current study, atopic patients reacted to more allergens on average, but the proportion of relevant contact reactions was similar whether atopic or not.

The possibility of some allergens being marginal irritants and increasing the chance of a false positive reaction should not be overlooked.¹⁴ For example, potassium dichromate 0.5% in petrolatum has been associated with irritant reactions previously.¹⁴ This may be more relevant in the context of an atopic, eczema-prone population, as in our group of patients. Some of the allergens used were topical preparations used neat, such as Canesten® cream, Vagisil® and Ovestin® (see Table 2 for ingredients). It is possible these may be marginal irritants when used neat; however, there is definitely value in testing these products in this context. Many patients reported use of these vulval topical products and standard, preservative and corticosteroid series did not test for all the constituents of these accurately. A positive result to one of the commonly used topical treatments for vulval pruritus was clinically relevant in the majority of cases.

Occlusion at this mucocutaneous site results in increased irritancy of substances normally well tolerated on other areas of the body.^{15–17} It has also been suggested that manufacturers may not take into consideration this increased susceptibility to irritant and allergic contact dermatitis of mucosal surfaces when performing pre-marketing testing.^{16,17}

Although most patients reported using topical corticosteroids, there were only two positive reactions to the corticosteroid allergens tixocortol pivalate and hydrocortisone-17-butyrate. These are representatives from groups A and D of the allergic contact dermatitis cross-reactive groups in corticosteroid patch testing.¹⁸ Budesonide was also tested, which is representative of group B,¹⁸ but none of our patients reacted to this. Tixocortol pivalate, a marker for hydrocortisone and methylprednisolone contact allergy, is a more common allergen in general, affecting approximately 1–5% of patch-tested populations.¹⁹ It is ideal to review a patient at day 7 also, to detect late corticosteroid reactions.¹⁹ Our patients were not reviewed at this time for practical reasons; however, they were asked to report any discomfort or symptoms suggestive of a late reaction.

Larger general population patch-test studies have concurred with our low rate of corticosteroid contact sensitivity.^{20,21} Both the Mayo Clinic and North American Contact Dermatitis Group reported patch-test positive rates of less than 3% for tixocortol pivalate and of 1.6% for budesonide in a general patch-test population.^{20,21}

Similarly low reaction rates for topical corticosteroids have been found in patch-test studies focusing on vulval dermatoses.^{2,5} Considering the widespread use of topical corticosteroids to irritated and inflamed skin and mucous membranes, it is reassuring that true allergic contact sensitivity appears to be relatively rare.

Behaviour and ablation habits were addressed in this study, and factors such as sexual activity and exposure to condoms was not associated with relevant contact allergy. A previous study has included intradermal testing to latex and partner's semen for some of their subjects.⁵ A high index of suspicion is needed to consider undertaking this more invasive and logistically difficult task.

Contact sensitization to numerous allergens may be relevant as a secondary phenomenon with patients presenting with vulval pruritus. The initial dermatosis may result in a compromised barrier and this flexural site appears to predispose to allergic sensitization. Our study shows an extended battery of allergens should be used in this clinical setting to ensure that preservatives and common topicals marketed for vulval pruritus are tested for contact sensitization potential. This study has reinforced the view that early and extended patch testing in the setting of vulval pruritus is useful in the management of patients with this difficult condition.

REFERENCES

- Lewis F, Shah M, Gawkrödger D. Contact sensitivity in pruritus vulvae: patch test results and clinical outcome. *Am. J. Contact Dermat.* 1997; **8**: 137–40.
- Marren P, Wojnarowska F, Powell S. Allergic contact dermatitis and vulvar dermatoses. *Br. J. Dermatol.* 1992; **126**: 52–6.
- Brenan J, Dennerstein G, Sfameni S, Drinkwater P, Marin G, Scurry J. Evaluation of patch testing in patients with chronic vulvar symptoms. *Australas. J. Dermatol.* 1996; **37**: 40–3.
- Rietschel R, Fowler J. Practical aspects of patch testing. In: *Fisher's Contact Dermatitis*, 5th edn. Philadelphia: Lippincott Williams & Wilkins, 2001; 9–26.
- Lucke T, Fleming C, McHenry P, Lever R. Patch testing in vulval dermatoses: how relevant is nickel? *Contact Dermatitis* 1998; **38**: 111–12.
- Fischer G. The commonest causes of symptomatic vulvar disease: a dermatologist's perspective. *Australas. J. Dermatol.* 1996; **37**: 12–18.
- Welsh B, Berzins K, Cook K, Fairley C. Management of common vulval conditions. *Med. J. Aust.* 2003; **178**: 391–5.
- Welsh B, Howard A, Cook K. Vulval itch. *Aust. Fam. Physician* 2004; **33**: 505–10.
- Nardelli A, Degreef H, Goossens A. Contact allergic reactions of the vulva: a 14 year review. *Dermatitis* 2004; **15**: 131–6.
- Salim A, Powell S, Wojnarowska F. Allergic contact dermatitis of the vulva – an overlooked diagnosis. *J. Obstet. Gynaecol.* 2002; **22**: 447.
- Goldsmith P, Rycroft R, White I, Ridley C, Neill S, McFadden J. Contact sensitivity in women with anogenital dermatoses. *Contact Dermatitis* 1997; **36**: 174–5.
- Virgili A, Levratti A, Zampino M, Corazza M. Are patch tests useful in plasma cell vulvitis? *J. Reprod. Med.* 2004; **49**: 105–7.
- Bauer A, Rodiger C, Greif C, Kaatz M, Elsner P. Vulvar dermatoses – irritant and allergic contact dermatitis of the vulva. *Dermatology* 2005; **210**: 145–9.
- Rietschel R, Fowler J Jr. Contact dermatitis and other reactions to metals. In: *Fisher's Contact Dermatitis*, 5th edn. Philadelphia: Lippincott Williams & Wilkins, 2001; 605–62.
- Farage M. Vulvar susceptibility to contact irritants and allergens: a review. *Arch. Gynecol. Obstet.* 2005; **272**: 167–72.
- Farage M, Maibach H. The vulvar epithelium differs from the skin: implications for cutaneous testing to address topical vulvar exposures. *Contact Dermatitis* 2004; **51**: 201–9.
- Farage M, Bjerke D, Mahony C, Blackburn K, Gerberick G. Quantitative risk assessment for the induction of allergic contact dermatitis: uncertainty factors for mucosal exposures. *Contact Dermatitis* 2005; **49**: 140–7.
- Warner S, Camisa C. Topical corticosteroids. In: Wolverson SE (ed.). *Comprehensive Dermatologic Drug Therapy*, 2nd edn. Philadelphia: Saunders Elsevier, 2007; 595–624.

19. Seukeran D, Wilkinson S, Beck M. Patch testing to detect corticosteroid allergy: is it adequate? *Contact Dermatitis* 1997; **36**: 127–50.
20. Krob H, Fleischer A, D'Agostino R, Haverstock C, Feldman S. Prevalence and relevance of contact dermatitis allergens: a meta-analysis of 15 years of published T.R.U.E. Test data. *J. Am. Acad. Dermatol.* 2004; **51**: 349–55.
21. Wetter D, Davis M, Yiannias J, Cheng J, Connolly S, el-Azhary R *et al.* Patch test results from the Mayo Clinic Contact Dermatitis Group, 1998–2000. *J. Am. Acad. Dermatol.* 2005; **53**: 416–21.