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REVIEW

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A systematic review of allergic and irritant contact dermatitis of the vulva: The most important allergens/irritants and the role of patch testing

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[Correction added on 27 December 2022, after first online publication: The ORCID for Hans Verstraelen has been added in this version.]

Abstract

Vulvar allergic contact dermatitis (vACD) and irritant contact dermatitis (vICD) are common and accompanied by a great burden on the patient's life. We aimed to review the existing literature on vACD and vICD in order to provide a comprehensive reference list of potential vulvar allergens and irritants, as well as to establish the role of patch testing therein. A systematic search was performed in Medline, Embase and Web of Science using a search string based on the PICO-format. The study protocol was registered at PROSPERO (CRD42021239527). Multiple allergens were identified and included metals, topical drugs, fragrances, preservatives, cosmetic constituents and rubber components. Not all positive reactions were, however, considered to be relevant. Patch testing is the primary tool for the identification of the causal allergens. Testing with standard series alone was proven to be insufficient. Little information about irritants was found. In the future, additional series and late readings should be considered in standard practice. Studies on vICD are scarce and further research is necessary. More population-based research should be performed.

KEYWORDS

allergic, contact dermatitis, contact dermatitis, eczema, irritant contact dermatitis, patch testing, vulvar contact dermatitis

1 | INTRODUCTION

Contact dermatitis of the vulva (vCD) is one of the most prevalent diagnoses in vulvar clinics. In the Oxford vulvar clinic for instance, it was estimated that 20%–30% of all (new) cases had contact dermatitis.[1,2] Although the exact incidence of vCD is unknown, irritant contact dermatitis (vICD) tends to be considerably more common than allergic contact dermatitis of the vulva (vACD), albeit vACD and vICD are not mutually exclusive and difficult to differentiate owing to overlapping and non-specific clinical features.[3]

The high prevalence of vACD and vICD relates to a number of intrinsic and extrinsic factors, including the anatomic proximity of the urogenital and gastrointestinal tract. Partly as a result, the vulva may be exposed to a variety of bodily fluids, including vaginal discharge, menstrual blood, urine, stool, sweat and sebum all of which may contribute to the development of vCD.[1,4] Arguably the best-studied model here is continuous exposure to urine, which may result in vCD due to the exposure to ammonia and the increased skin moisture.[5] As such, urinary incontinence is considered a prominent clinical risk factor. Similarly, faecal material has well-known directly irritating properties due to the presence of faecal enzymes.[1] Extrinsic factors, such as occlusion by underwear, sanitary pads, skin-to-skin contact and friction from sexual activity, as well as contact with clothing may further enhance the susceptibility of the vulvar skin to irritants and allergens.[4,6]

In addition, as the vulva is an intimate region, contact dermatitis can have a substantial impact on the patient's psychosexual and psychological well-being. Vulvar contact dermatitis may further affect

Sander Vandeweege and Britt Debaene contributed equally to this study.

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activities of daily living.[7,8] Finally, due to cultural taboos and feelings of embarrassment, many women avoid consulting a healthcare provider with their concerns and choose to self-medicate with over the counter bought products. This plays a major role in the underdiagnosing of vACD/vICD, as self-treatment is a potential source of vulvar irritation and sensitization. The other main factors in underdiagnosing vACD and vICD are the poor awareness, under-recognition and misdiagnosis of vulvar disorders by healthcare providers.[3,4]

The aim of this systematic review was twofold. Firstly, the existing literature was examined for all allergens and irritants reported to cause vACD and vICD, respectively, in order to provide a comprehensive reference list of potential vulvar allergens and irritants. Since the main treatment for vACD and vICD is the avoidance of all putative irritants and specific allergens, this review can be most useful.[9] Furthermore, as patch testing is a widely used tool in the diagnostic process of allergic contact dermatitis, we have examined the validity of this testing method for the diagnosis of vACD.

2 | MATERIALS AND METHODS

A systematic review of the literature was performed. Medline, Embase and Web of Science were searched up to February 12, 2021. The search string for each database can be found in Appendix S1. The strings are based on the PICO-format (Population, Intervention/Exposure, Comparison and Outcome) and separated into concepts in order to find studies in women (Population) with allergic or irritant contact dermatitis of the vulva (Outcome) following exposure to allergens or irritants (Exposure). Furthermore, patch testing was used as a concept since this review wanted to identify the diagnostic value of patch testing in women with allergic contact dermatitis of the vulva. Different combinations of relevant terms were used. Search terms were selected using MeSH and Emtree. Moreover, key articles were explored in order to identify all possible synonyms. The study protocol was registered with the International Prospective Register for Systematic Reviews (https://www.crd.york.ac.uk/prospero/) under reference CRD42021239527.

2.1 | Study selection

The PRISMA guidelines were used in order to conduct the selection of the studies.[10] After applying the search strategy, the identified articles were stored in EndNote and after duplicate removal, screening of the identified records was performed by two independent reviewers (Sander Vandeweege and Britt Debaene). First, a selection was made based on title. Afterwards, the two reviewers compared their selection and discussed. This procedure was repeated for the selection based on abstract and full-text. No conflicts arose during this process. Inclusion criteria for this systematic review were: women with symptoms of allergic or irritant contact dermatitis of the vulva after exposure to allergens or irritants, respectively. Reviews, case reports, guidelines and letters were excluded. Conference abstracts and short communications were checked for full-text papers and when absent, the articles were excluded. Studies that were not written in Dutch, English or French, animal studies and studies that lack relevance for this systematic review (studies that do not involve the vulva, allergens/irritants or patch testing, etc.) were also excluded. Studies that include both men and women and lack separate data for women were excluded as well. Because no weighted meta-analysis was performed, only studies containing 20 or more vulvar patients were included in order to avoid that results of studies with a limited amount of participants got the same weight as studies with larger cohorts. No restrictions were made based on publication date. Reference lists of eligible studies were screened for additional relevant articles.

2.2 | Data extraction, data synthesis and risk of bias (quality) assessment

The following data were extracted: study design and methodology, number of participants, demographic data, allergens causing vACD (identified by a positive patch test), irritants causing vICD and, when available, data relating to the diagnostic value of patch testing in this context. The process of data extraction was performed independently by two reviewers (Sander Vandeweege and Britt Debaene) and discussed afterwards. The two reviewers compared the extracted information and discussed whether there were discrepancies or disagreements. Any disagreement would have been resolved through discussion and communication with a third author, but no conflicts arose. Afterwards, the aforementioned extracted data were synthesized. For the risk of bias (quality) assessment, the Cochrane risk of bias tool (RoB 2) was used for the assessment of randomized controlled trials (RCTs) and the AXIS tool was used for the assessment of cross-sectional studies.[11,12] The assessment was independently performed by the two reviewers and discussed afterwards.

Since there was no template available for the graphical presentation of the results of the risk of bias assessment of the cross-sectional studies (AXIS), a customized visual representation was made. The results are displayed in Figure 2. The '+' sign was used when a certain criterion was met and '−' when it was not met. The results of the RoB 2 tool, that was used for the risk-of-bias assessment of the single RCT, are presented in Figure 3. For question seven of the AXIS-tool, 'not applicable' was given when there was a retrospective study design, since there cannot be non-responders. The study performed by Vermaat et al. has a retrospective and a prospective part, therefore the combination of 'not applicable' with 'no information' was noted.[13] For question 20, a 'no' was scored when no information was given concerning ethical approval.

3 | RESULTS

3.1 | Study selection

The literature search yielded 580 records of which 377 were screened. During the title and abstract reviewing process 324 articles

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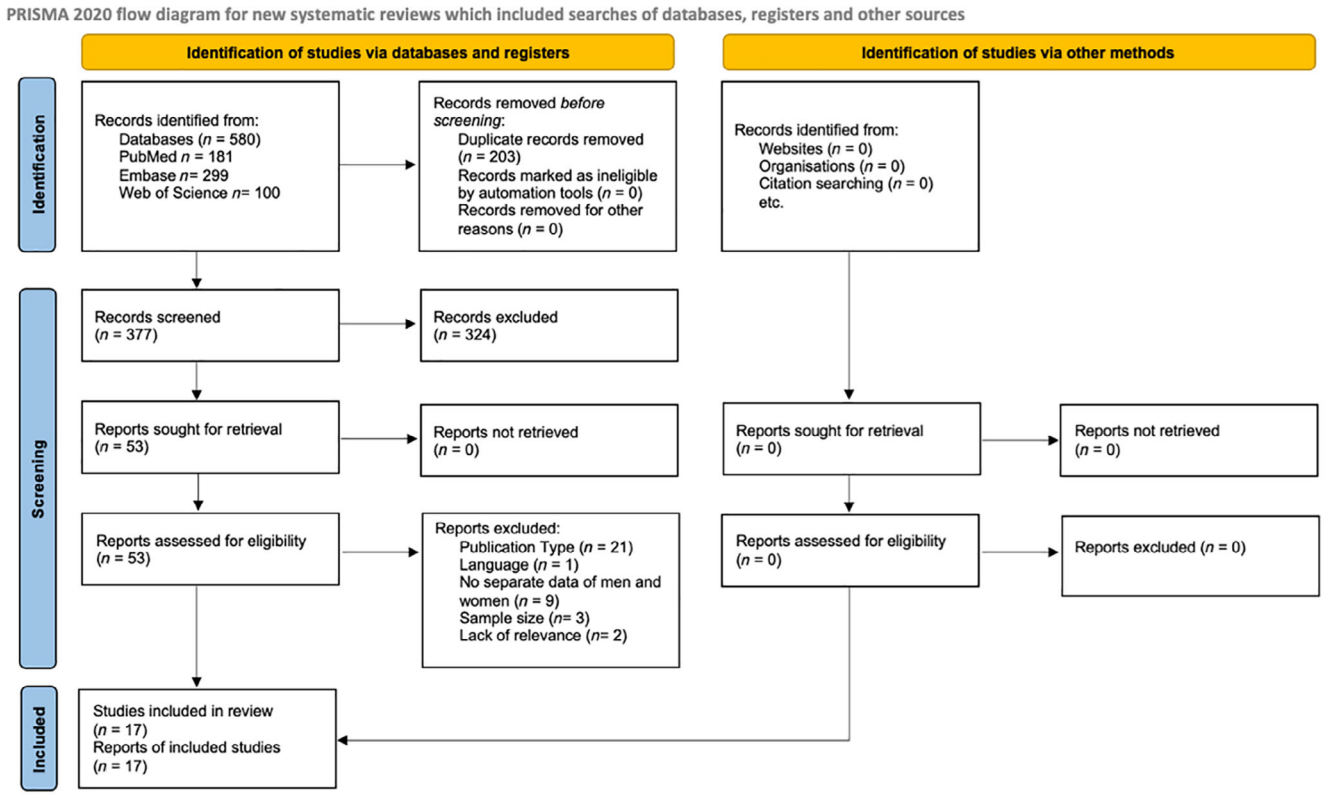

FIGURE 1 Overview of the systematic literature selection. Source: Page et al.[10]

were excluded. Afterwards, 53 full-texts were assessed for eligibility. Finally, 17 studies published between January 1992 and December 2020 met the inclusion criteria. Reasons for exclusion are reported in the PRISMA flow diagram (Figure 1).

3.2 | Study characteristics

Of the included studies, 16 studies had a cross-sectional design, of which nine were retrospective in which databases were used to conduct the study.[13–21] One randomized controlled trial was included.[22] Most studies were single-centred and almost all the studies ($n = 15$) concerned allergic contact dermatitis. Of the eligible studies, 10 were performed in Europe,[13–15,17–19,22–25] three in North-America,[20,21,26] three in New Zealand/Australia[16,27,28] and one in Turkey.[29] All publications were written in English. The total number of study patients in all the studies combined was 1363. All ages were represented in the studies, ranging from 1 to 92 years. The mean age of the total study population was not always provided. The mean age ranged between 35.3 and 59.4 years in the studies that provided this information ($n = 13$).[13–20,23,25,27–29] Of all studies, 14 included post-menopausal women.[13–23,25,28,29] Al-Niaimi et al. conducted the largest study with a total of 282 patients with vulvar symptoms that underwent patch testing.[14] Only three studies mentioned ethnicity, with over 90% of the patients included in these studies being Caucasian. The duration of the symptoms was mentioned in seven studies, with symptoms often lasting for several years.[13,14,20,23,27–29] Some patients had a pre-existing vulvar disease of which the most prevalent diagnoses were: vulvar dermatitis, lichen sclerosus, lichen planus, lichen simplex chronicus, vulvodynia, candidiasis and psoriasis.[14–16,18–21,23,25,27–29]

3.3 | Risk of bias of included studies

The results of the risk of bias assessment can be found in Figure 2 for the cross-sectional studies and Figure 3 for the RCT. In none of the cross-sectional studies was the sample size justified by the authors.[13–21,23–29] The sampling frame was considered not representative for the total population in 11 of the 16 cross-sectional studies.[13,15–20,23,25,27,29] There was a lack of basic demographic data in half of the studies.[13–16,18,19,25,26] Limitations of the study were not discussed in 10 studies.[13,18–20,24–29] Ethical approval or patients' consent was missing/not mentioned in 11 studies.[13–15,17–19,23–25,27,29] Concerning the single RCT, risk of bias was considered high for the measurement of the outcome subjective sensory effects. Risk of bias for the selection of the reported results was considered high for all three outcomes (erythema of the external genitalia, genital tissue wetness and subjective sensory effects).[22]

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Questions:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Al-Niaimi et al.	+	+	-	+	+	+	N.A. [a]	+	+	N.A.	-	-	N.A.	N.A.	+	N.A.	+	+	+	-
Batchelor et al.	+	+	-	+	-	+	N.A.	+	+	N.A.	-	-	N.A.	N.A.	+	N.A.	+	+	+	-
Brenan et al.	-	+	-	-	-	-	N.I. [b]	+	+	N.A.	+	+	N.A.	N.A.	+	N.A.	+	-	+	-
Cheng et al.	+	+	-	+	-	+	N.A.	+	+	+	+	-	N.A.	N.A.	+	-	+	+	+	+
Corazza et al.	+	+	-	+	-	-	N.I.	+	+	N.A.	+	+	N.A.	N.A.	+	+	+	+	+	-
Crone et al.	+	+	-	+	+	+	N.I.	+	+	N.A.	-	+	N.A.	N.A.	+	N.A.	+	-	+	-
Gilissen et al.	+	+	-	+	-	+	N.A.	+	+	+	+	+	N.A.	N.A.	+	-	+	+	+	-
Haverhoek et al.	+	+	-	+	+	+	N.I.	+	+	N.A.	+	+	N.A.	N.A.	+	N.A.	+	-	+	+
Lewis et al.	+	+	-	+	-	+	N.A.	+	+	N.A.	-	-	N.A.	N.A.	+	N.A.	+	-	+	-
Marren et al.	-	+	-	+	-	+	N.I.	+	+	N.A.	-	-	N.A.	N.A.	+	N.A.	+	-	+	-
Nardelli et al.	+	+	-	+	-	+	N.A.	+	+	N.A.	-	-	N.A.	N.A.	+	N.A.	+	-	+	-
O'Gorman et al.	+	+	-	+	-	+	N.A.	+	+	+	+	+	N.A.	N.A.	+	+	+	-	+	+
Utas et al.	+	+	-	+	-	+	N.I.	+	+	N.A.	+	+	N.A.	N.A.	+	N.A.	+	-	+	-
Vermaat et al.	+	+	-	+	-	+	N.A./N.I.	+	+	N.A.	+	-	N.A.	N.A.	+	N.A.	+	-	+	-
Warshaw et al.	+	+	-	+	+	+	N.A.	+	+	+	-	+	N.A.	N.A.	+	+	+	+	+	+
Wilhelm et al.	+	+	-	+	+	+	N.I.	+	+	+	-	-	N.A.	N.A.	+	+	+	-	+	+

a = Not applicable, b = No information.

FIGURE 2 Results of the risk of bias assessment of the cross-sectional studies

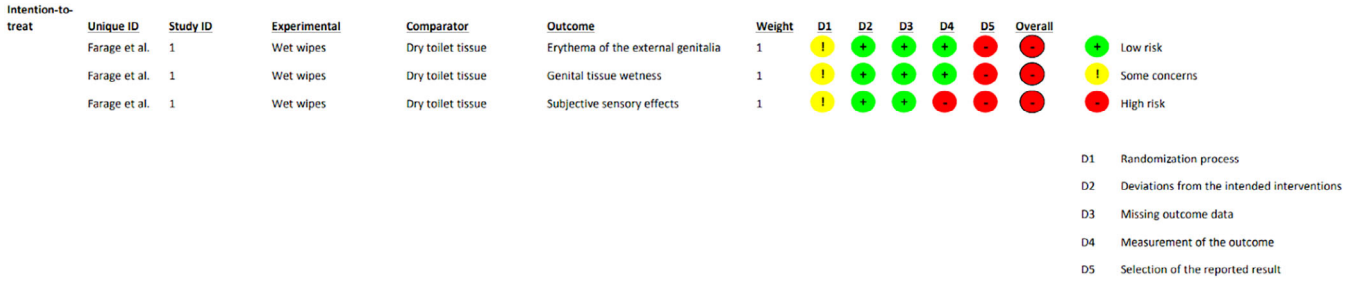

FIGURE 3 Results of the risk of bias assessment of the randomized controlled trial

3.4 | Synthesis of results

3.4.1 | Allergic contact dermatitis

General results and allergens

For this systematic review, all included patients were patch tested and the positive reactions that were considered relevant are displayed. Reactions were considered relevant when the allergen was used by the patient and clinical improvement occurred when the allergen was avoided.[18,28] The synthesis of the results, including a description of the study population and age distribution, is displayed in Table 1. The allergens that gave positive reactions and the interpretation of relevance can be found in Table 2. Some allergens had multiple uses, but for practical reasons these were only mentioned in one allergen category. The allergens that were most frequently identified across studies were nickel and cobalt, topical drugs (including corticosteroids), fragrances and preservatives. The percentage of patients that had one or more positive reaction ranged from 38% in the study by Nardelli et al. up to 81.4% in the study by Haverhoek et al.[19,28] The most common allergens that were deemed relevant were corticosteroids, fragrances and preservatives. Of positive patch test reactions, relevance ranged from 13% in the study by Vermaat et al. to 49% of the reactions in the studies by Al-Niaimi et al. and Lewis et al.[13,14,18] Cheng et al. did not provide separate information of the relevance of the tests for men and women, therefore this study could not be included in the 'relevance' section of Table 2.[16] Furthermore, the study by Brenan et al. did not mention relevance.[27]

3.4.2 | Irritant contact dermatitis

Only two of the included studies researched irritant contact dermatitis. Farage et al. conducted a randomized prospective trial to assess the effects of feminine hygiene wet wipes on vulvar skin in pre- and post-menopausal women.[22] They compared dry toilet tissue to wet wipes. No statistically significant differences were observed in mean erythema scores between the treatment group and the control group, this at any site or any evaluation point.[22] Wilhelm et al. researched the effect on the skin of menstrual pads containing sodium bicarbonate. No clinical signs of irritation were observed.[26]

3.4.3 | Patch testing

Most authors performed the patch testing process in accordance with the guidelines of the International Contact Dermatitis Research Group

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TABLE 1 Synthesis of the results

Author	*N*	Mean age in y (SD)	Population	Top five common allergens (percentage of total tested population)	Top 5 relevant allergens in absolute numbers (percentage of respective positive tests)	Number of positive reactions	Number of relevant reactions
Al-Niaimi et al. (2014)	282	51 y Range: 14–89 y	Women with vulvar dermatitis or symptoms of pruritus patch tested in their tertiary referral unit	1. Nickel 2. Cobalt 3. Neomycin 4. Fragrance mix 5. Balsam of Peru (No percentages given)	1. Neomycin 2. Balsam of Peru 3. Fragrance mix	• ACD diagnosis in 54% • Reaction to 2–4 allergens: 39% • More than four allergens: 8% • 6% reacted to own products	• Relevant reactions: 49%
Batchelor et al. (2003)	240	42 y Range: 5–88 y	Female patients with dermatoses in the perineal area	1. Medicaments (25%) 2. Fragrances (13%) 3. Cosmetic components (4%) 4. Nylon dyes (2%) 5. Rubber (2%)	1. Medicaments (83%) 2. Fragrances (75%) 3. Cosmetic components (56%) 4. Nylon dyes (80%) 5. Rubber components (80%)	• 41.3% had positive reactions	• Relevant reactions: 32,9% had 1 or more • 36% of patients with LS, 14% of patients with pruritus vulvae
Brenan et al. (1996)	50	38.8 y	Mainly patients presenting with pruritus and vulvodynia	1. Nickel (22%) 2. Fragrances (12%) 3. Ethylenediamine (8%) 4. Caine mix (6%) 5. Cobalt (6%)	No information about relevance	• 42% had positive reactions • Reaction to 1 allergen: 20% • 2 allergens: 12% • 3 or more: 10%	No information
Cheng et al. (2020)	37	51 yy (17.9)	Patients with dermatoses of the anogenital region	1. Nickel sulphate (22%) 2. Fragrance mix I (16%) 3. *Myroxylon Pereirae* (16%) 4. Cobalt chloride (14%) 5. Dodecyl gallate (11%)	No information about relevance	• 56.8% had positive reactions • Mean number of reactions: 1.66 • 8.1% reacted to own products	No separate data for men and women
Corazza et al. (2016)	66	59.43 y (14.58) Range: 21–86 y	Women with itching vulvar inflammatory diseases	1. Nickel sulphate (17%) 2. Fragrance mix (8%) 3. *Myroxylon Pereirae* (8%) 4. MCI/MI (6%) 5. Fragrance mix II (5%)	1. *Myroxylon Pereirae* (80%) 2. Fragrance mix I (40%) 3. Fragrance mix II (67%) 4. MCI/MI (50%) 5. Cocamidopropyl betaine (100%)	• SIDAPA series: 40.9% had positive reactions • Botanical series: two positive reactions • One positive reaction to own products	• Relevant reactions: 21.2% had 1 or more

(Continues)

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TABLE 1 (Continued)

Author	N	Mean age in y (SD)	Population	Top five common allergens (percentage of total tested population)	Top 5 relevant allergens in absolute numbers (percentage of respective positive tests)	Number of positive reactions	Number of relevant reactions
Crone et al. (2000)	35	45 y Range: 22–66 y	Patients with a clinical diagnosis of vulvar dermatitis (new referrals or diagnosed patients)	1. Nickel sulphate (16%) 2. Balsam of Peru (13%) 3. Formaldehyde (13%) 4. Fragrance Mix (13%) 5. Quaternium 15 (13%)	1. Fragrance mix (100%) 2. Balsam of Peru (75%) 3. Formaldehyde (75%) 4. Quaternium 15 (75%) 5. Sodium Metabisulphite (100%)	• 43% had positive reactions • 17% had one positive reaction • 26% had multiple reactions	• Relevant reactions: 26% had 1 or more • 23% had multiple
Gilissen et al. (2020)	30	50 y Median: 51.5 y Range: 1–78 y	Patients suffering from iatrogenic dermatitis ((peri)anal/genital area)	Common and relevant: 1. Lidocaine (13%) 2. Benzoic acid (7%) 3. Budesonide (7%) 4. Hydrocortisone (acetate) (7%) 5. Wool alcohols (7%)	See previous column	• All patients tested positive for one or more allergen	• All patients had one or more relevant reaction
Haverhoek et al. (2008)	43	42 y Range: 20–80 y	Patients with the primary complaint of vulvar pruritus	1. Nickel 2. Cobalt 3. Tea tree oil (No information about frequency)	1. Vagisil 2. Clioquinol 3. Benzalkonium chloride (No information about frequency)	• 81.4% had positive reactions • Reaction to 1 allergen: 26% • 4 or more: 26%	• Relevant reactions: 44% had one or more
Lewis et al. (1997)	121	43.7 y	Patients with vulvar problems referred to the clinic	Common and relevant: 1. Lanacane (14%) 2. Fragrance mix (13%) 3. Neomycin (7%) 4. Balsam of Peru (6%) 5. Cinchocaine (3%)	See previous column	• 58.7% had positive reactions	• Relevant reactions: 49% • 44% of patients with lichen sclerosus
Marren et al. (1992)	135	51 y Range: 14–88 y	Patients with persistent vulvar symptoms, referred from the vulva clinic	1. Nickel (11%) 2. Balsam of Peru (9%) 3. Ethylenediamine (8%) 4. Fragrance mix (7%) 5. Neomycin (7%)	1. Ethylenediamine (91%) 2. Balsam of Peru (83%) 3. Fragrance mix (89%) 4. Framycetin (88%) 5. Neomycine (78%)	47% had one or more positive reactions 23% had one positive reaction 24% had multiple positive reactions	Relevant reactions: 29%
Nardelli et al. (2004)	92	49 y Range: 7–92 y	Patients with vulvar complaints referred for patch testing	1. Benzoic acid (29%) 2. Butylhydroxyanisole (29%) 3. Hydrocortisone acetate (27%) 4. Triamcinolone acetonide (27%) 5. Hydrocortisone 17 butyrate (20%)	1. Triamcinolone acetonide (75%) 2. Benzoic acid (100%) 3. Butylhydroxyanisole (100%) 4. Hydrocortisone acetate (50%) 5. Hydrocortisone butyrate (67%)	• 38% had 1 or more positive reaction • 14% had one positive reaction • 24% had multiple positive reactions	No clear information

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TABLE 1 (Continued)

Author	*N*	Mean age in y (SD)	Population	Top five common allergens (percentage of total tested population)	Top 5 relevant allergens in absolute numbers (percentage of respective positive tests)	Number of positive reactions	Number of relevant reactions
O'Gorman et al. (2013)	90	52.2 y Range: 12.9–84.3 y	Patients presenting with vulvar symptoms	1. Gold sodium thiosulphate 2% (38%) 2. Gold sodium thiosulphate 0.5% (21%) 3. Benzocaine (12%) 4. Nickel sulphate (10%)	1. Natural fragrance mix (86%) 2. Balsam of Peru (63%) 3. Benzocaine (71%) 4. Fragrance mix (50%) 5. Quaternium 15 (67%)	• 69% had one or more positive reactions • 23% had one positive reaction • 46% had multiple positive reactions • Average number of positive reactions was 2.5	• 39% had a relevant reaction • Average number of relevant reactions was 1.25
Utas et al. (2008)	50	39.9 y[9] Range: 22–62 y	Women with vulvar pruritus who were evaluated for vulvar dermatoses	Common and relevant: 1. Fragrance mix (4%) 2. *Myroxylon Pereirae* (4%)	See previous column	• 52% had one or more positive reaction	• 16% had one or more relevant reaction
Vermaat et al. (2008)	53	35.3 y Median: 32.5 y Range: 16–64 y	Women with chronic anogenital complaints	1. Nickel (34%) 2. Fragrance mix I (15%) 3. Curry mix (Djawa) powder (8%) 4. Cobalt (6%)	Spices (38%) Fragrance mix (13%) Hydroxyisohexyl 3-cyclohexene carboxyaldehyde (50%) Methyldibromo glutaronitrile (33%) Primin (100%)	66% had one or more positive reaction 34% had one positive reaction 32% had multiple positive reactions	13% had one or more relevant reaction
Warshaw et al. (2008)	39	No Information	Patients with anogenital allergic contact dermatitis	Common and relevant: 1. *Myroxylon Pereirae* (28%) 2. Fragrance mix (23%) 3. Nickel sulphate (15%) 4. Benzocaine (10%) 5. Quaternium 15 (10%)	See previous column	No information	No information

Abbreviations: MCI/MI, methylchloroisothiazolinone/methylisothiazolinon; *N*, number of participants; SD, standard deviation; y, years.

or the European Society of Contact Dermatitis.[13,16,17,23,27] Patches were usually applied on the upper back.[13,17,23] Frequently used series included the European standard series,[13–15,17–19,25,28,29] corticosteroid series,[14,25,27,28] preservatives,[14,18,25,27–29] a medicament battery,[18,23,25,27–29] patients' own products[13–15,17,19,23,25,29] and cosmetics.[18,19,25,29]

Readings were performed on day 2, sometimes day 3, and day 4.[13–19,23,25,27,29] O'Gorman et al. and Haverhoek et al. performed readings on day 3 and day 5.[20,28] Late readings were performed on day 6 or day 7 in order to identify a late corticosteroid allergy.[13,16,17,19] Corazza et al. used the Società Italiana Dermatologia Allergologica Professionale ed Ambientale

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TABLE 2 Overview of haptens with positive reactions and their relevance

Allergens that tested positive	Studies with positive reactions	Studies with relevant reactions
Metals		
Cobalt	13,14,16,19,20,23–25,27,28	20
Copper	16	
Gold sodium thiosulphate	16,20	20
Nickel	13,14,16,19–21,23–25,27–29	20,21,23,29
Palladium chloride	19	
(Topical) Medicaments		
Antibacterials		
Bacitracin	20,21	21
Clindamycin	20	20
Neomycin	14,15,17,19–21,24,27	14,15,17,19–21,24
Framycetin	14,15,24,25	14,15,24,25
Fucidine	25	25
Streptomycin	29	29
Sulphanilamide	19	
Quinoline mix	15,23,25	15,23,25
Clioquinol	15,18,28	15,18,28
Chloramphenicol	25	25
Chlorquinaldol	15	15
Antiseptics		
Benzalkonium chloride	16,20,24,28	20,24,28
Chlorhexidine	15	15
Hexylresorcinol	20	
Povidone iodine	17	17
Triclosan	27	
(Local) Anaesthetic		
Amethocaine	15	15
Benzocaine	15,16,18–21	15,20,21
Bupivacaine hydrochloride	19	
Butoform	19	
Caine mix	14,15,27	14,15
Cinchocaine	14,15,18,19,21	14,15,18,19,21
Lidocaine	15,17,19	15,17,19
Mepivacaine hydrochloride	19	
Tetracaine hydrochloride	23	23
Corticosteroids		
Betamethasone diproprionate	17	17
Budesonide	15,17,19,23,27	17,23
Clobetasol proprionate	19,21,25	21,25
Corticosteroid mix	23	23
Hydrocortisone	17	17
Hydrocortisone acetate	17,19,23	17,19,23
Hydrocortisone butyraat	19,21	19,21
Prednisolone caproate	19	19
Tixocortol pivalate	15,19–21,24,25	15,20,21,24,25
Triamcinolone acetonide	17,19	17,19

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TABLE 2 (Continued)

Allergens that tested positive	Studies with positive reactions	Studies with relevant reactions
Antimycotic medication		
Clotrimazole	20	20
Econazole nitrate	19	19
Miconazole	19,20	19
Isoconazole	19	19
Terconazole	20	20
Tioconazole	20	20
Tolnaftate cream	16	
Nonsteroidal anti-inflammatory drugs		
Bufexamac	17	17
Etofenamate	19	
Immunosuppressants		
Pimecrolimus cream	16	
Topical Hormones		
Conjugate oestrogen	20	20
Dienoestrol cream	27	
Estradiol	19	19
Testosterone	19	19
Testosterone propionate	17	17
Other topical products		
Acyclovir	17	17
Benzoyl peroxide	16,19	
Etofenamate	19	
Hydrocortisone, clotrimazole cream	16	
Methyl salicylate	29	29
Fragrances		
Cinnamal	21	21
Evernia prunastri	13	
Fragrance mix I	13–21,23–25,27,29	13–15,17,19–21,23–25,29
Fragrance mix II	20,23	20,23
Hydroxyisohexyl 3-cyclohexene carboxaldehyde	13,23	13,23
Jasmine absolute	13	
Lavender absolute	13	
Lemongrass oil	13	
Limonene oxidized	19	
Myroxylon Pereirae (Balsam of Peru)	13–16,18–21,23–25,27,29	14,15,19–21,23–25,29
Narcissus absolute	13	
Natural fragrance mix	20	20
Spices		
Cayenne pepper powder	13	
Coriander powder	13	13
Curry mix (Djawa) powder	13	13
Nutmeg powder	13	13
Onion powder	13	13
Pepper (white) powder	13	
Peppermint oil	13	13

(Continues)

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TABLE 2 (Continued)

Allergens that tested positive	Studies with positive reactions	Studies with relevant reactions
Preservatives		
Benzoic acid	13,17,19,20	17,19
Butyl-4-hydrobenzoate	16	
Chloroacetamide	25	25
Chlorocresol	15,16,19	15,19
Diazolidinyl urea	16,25	25
DMDM hydantion	20,24	20,24
Dodecyl gallate	16,29	29
Euxyl K400 (Phenoxyethanol and methyldibromoglutaronitrile)	19	
Formaldehyde	16,20,23–25,27	20,23–25
Hexahydro-1 3 5-tris(2-hydroxyethyl)-s-triazine	16	
Imidazolidinyl urea	16,20,25	20,25
Methylchloroisothiazolinone/Methylisothiazolinone	15,19–21,23,29	15,19–21,23,29
Methyldibromoglutaronitrile	13,15,16,20,23	13,15,20
Paraben mix	15,19–21,25,29	15,19–21,25,29
Quaternium 15	15,16,20,21,23–25,27	15,20,21,23–25
Sodium metabisulphite	13–16,24,25	14,15,24
Thiomersal	13,16,25,27	
2-Bromonitropropane-1,3-diol	15,19–21	15,19,21
2-phenoxyethanol	13	
Other cosmetic constituents		
Butylhydroxyanisole	17,19	17,19
Butylhydroxytolueen	25	
Cetyl alcohol (hexadecanol)	17	17
Cocamidopropyl betaine	16,20,23,29	20,23,29
Coconut diethanolamide	16	
Glyceryl thioglycolate	20	20
Isopropyl myristate	25	
Lanolins/Wool Alcohols/Amerchol L101	15,17,19,21,25,27	15,17,19,21,25
Octyl gallate	24,29	29
p-Phenylenediamine	13,16,18–20,24,25,27	20,24
Polyethylene glycol-1000-monocetyl ether	17	17
Propylene glycol	19–21,25	19–21,25
Stearyl alcohol	25	25
Sodium lauryl sulphate	20	20
Tosylamide formaldehyde resin (Toluene sulphonamide formaldehyde resin)	20,24	20
Disperse dyes		
p-Aminoazobenzene	15,19	15
Disperse orange 1	19	
Disperse orange 3	15,20	15,20
Disperse red 1	15	15
Disperse blue 106	13,20,27	20
Disperse blue 124	20	20
Disperse blue 153	19	
Rubber components/industry		
Black rubber mix	25	
Carba mix	15,19–21	15,20,21

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TABLE 2 (Continued)

Allergens that tested positive	Studies with positive reactions	Studies with relevant reactions
Diaminodiphenylmethane	19	
Diphenylthiourea	19	
Isopropyl phenyl para-phenylenediamine	19	
Mercaptobenzothiazole	25	
Mercapto mix	19,25	
Naphtyl mix	19	
Thiuram mix	13,15,19,24,25	15,24
Botanicals		
Arnica montana	23	23
Calendula	17	17
Compositae mix	13,20,23	23
Primin	13,19,25	13
Roman chamomile	17	17
Sesquiterpene lactone mix	13	
Tea tree oil	28	
Other		
Cetearyl alcohol	15	15
Colophonium	16,19,25	
Ethyl acrylate	20	
Ethylenediamine	15,17–21,25,27	15,17,19–21,25
Epoxy resin	19,24	
Nonoxynol 9	17	17
Phosphorus sesquisulphide	25	
Potassium dichromate	14,16,19,20,23,25,27	
P-tert-butylphenol formaldehyde resin	13,16,20,27	20
Sorbitan monooleate	16	
Sorbitan sesquioleate	17	17
Patients' own products		
Aluminium starch octenyl succinate	13	
Benoxyl 5 cream (benzoyl peroxide 5%)	25	25
Canesten (clotrimazole 1%)	25	25
Carbo-dome cream (coal tar solution 10%)	25	25
Clearsun day/night cream	13	
Eurax cream (crotamiton 10%)	25	25
KY Jelly	27	
Lanacane (3% benzocaine)	18	
Proctocedyl ointment (hydrocortisone 0.5%, cinchocaine hydrochloride 0.5%)	25	25
Replens	20	
Sanex Bodymilk	13	13
Savlon (10% solution) (Chlorhexidine gluconate 1.5%, cetrimide 15%)	25	25
Vagisil (benzocaine 5%, resorcinol 2%)	27,28	28
Xylocaine ointment (lignocaine 5%)	25	25
Nail varnish in paraffin	27	

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(SIDAPA) series and Warshaw et al. used the North-American Contact Dermatitis Group (NACDG) standard series and a TRUE test (Allerderm Laboratories, Inc.).[21,23] Batchelor et al. found that using the European Environmental and Contact Dermatitis Research Group (EECDRG) series alone would have missed 31.1% of the cases.[15]

4 | DISCUSSION

To our knowledge, this is the first systematic review on allergic and irritant contact dermatitis of the vulva. Therefore, it can yield valuable insights in these two conditions. The major findings of this systematic review are that there is a variety of allergens that are capable of causing allergic contact dermatitis of the vulva and that, in addition to patient history and clinical presentation, patch testing is a widely used tool in the diagnostic process of vACD. However, we failed to identify studies that compared patch testing with other diagnostic tools, and hence, the accuracy of patch testing in this setting could not be determined. This review was also not able to identify common irritants causing vICD. We further discuss the primary findings.

4.1 | Allergic contact dermatitis

Overall, 38%–81.4%[19,28] of patients in our review reacted to one or more allergen, which is in line with the recent findings of Woodruff et al. who reported a range of 39%–78%.[4] However, as all the studies were performed in secondary or tertiary referral centres the prevalence of vACD in the general population remains elusive. Furthermore, it is important to note that not all positive reactions were considered clinically relevant. The incidence of relevant reactions for patients presenting with vulvar complaints ranged from 13% to 49%.[13,14,18] Woodruff et al. previously estimated 16%–54% of positive reactions in this context to be relevant.[4]

4.1.1 | Allergens and allergen avoidance

Nickel allergy was common in most studies, although the relevance of this finding remains debatable, since direct contact with nickel in the genital area is not commonly expected to occur. Dietary nickel intake should however be taken into consideration, as avoidance has anecdotally been reported to resolve anogenital symptoms.[30,31] Presumably through a reduction of the urinary nickel excretion. Another metal that was frequently associated with positive reactions is cobalt. Relevance is again questionable, but a study by Veien et al. showed that an oral challenge with cobalt in patients with a positive patch test can induce a flare of the dermatitis.[32]

Positive reactions to multiple classes of topical drugs were also common and included reactions to antibiotics, neomycin, framycetin, clioquinol and quinoline mix. However, the relevance of these specific antibiotics has been decreasing over the years since usage of these products is diminishing.[33] Contact allergy to corticosteroids was also frequent and obviously particularly relevant, considering the common use of topical corticosteroids in vulvar disease.[3,4,34] Contact allergy to local anaesthetics was another frequent occurrence, and of defined interest here, as local anaesthetics and topic hemorrhoid preparations are typical OTC products frequently and repeatedly used to relieve vulvar symptoms. Other topical drugs causing positive reactions included antiseptics, antimycotics, non-steroidal anti-inflammatory drugs, immunosuppressants and topical hormones.

The common finding of positive reactions to Fragrance mix I and *myroxylon pereirae* (Balsam of Peru) was not unexpected and exposure to fragrances may relate to use of cosmetics, perfumes, fabric, scented toilet tissue, haemorrhoid creams, (topical) drugs, female hygiene products, etc.[34]

Preservatives also remain of concern, despite evolving regulatory restrictions. Formaldehyde releasing preservatives can be found in up to 25% of the cosmetic products in the United States and Europe.[34] The non-formaldehyde releasing preservative methyldibromo glutaronitrile has been banned by the European Commission from leave-on products in 2003 and later, in 2007, from rinse-off products. Sensitization remains high in Europe however, since it is still used in other, non-regulated sources like industrial materials,[35,36] while in the United States it is still used in skin care products.

Other cosmetic constituents such as para-phenylenediamine (PPD) may cause cross-reactions with para-aminobenzoic acid (sunscreens), sulphonamides/sulphonylureas (medication), azo dyes (clothes), benzocaine/tetracaine (local anaesthetics), etc. Patients with sensitization to PPD had a higher risk of simultaneous reaction to other chemically related dyes, such as clothing dyes in the study performed by Mukkanna et al.[37] Disperse dyes, including Disperse Orange 3, Disperse Blue 106 and Disperse Blue 124, were another recurrent allergen class. Possible exposure to these dyes came from underwear and patients with allergic reactions to these agents should therefore be advised to avoid dark, synthetic clothes and wear clothing made out of non-synthetic fibres such as cotton.[38]

It may be added, that in a retrospective analysis, Wakelin et al. found that of all patients who were patch tested to wool alcohols, the rates of contact allergy to lanolin (found in cosmetics, shampoo, shaving creams and topical medicaments[39]) were second highest in patients presenting with dermatitis of the anogenital area.[40]

Of interest are also rubber additives and sulphur containing vulcanizers such as thiuram mix, carba mix and mercapto mix in particular. Vulvar exposure to these allergens may occur through condoms or other contraceptives. The additives typically cause a type IV allergy, in contrast to natural rubber (latex) itself, which causes a type I allergy.[41]

Some studies identified botanical allergens such as chamomile, tea tree oil, *arnica montana*, calendula, primin and the compositae mix as sensitizers. Tea tree oil is the most common sensitizer among essential oils and is especially potent when oxidized,[42] whereas reactions to the compositae family of plants (chamomile, calendula, *arnica montana*) are rare.[43] In cases where the reactions were considered relevant to vCD, it was used for multiple skin conditions (acne, eczema, …).[42]

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Concerning spices, the study by Vermaat et al. found that spices were a common culprit, giving multiple relevant positive reactions.[13] Spices involved were cayenne pepper powder, coriander powder, curry mix (Djawa) powder, nutmeg powder, onion powder, pepper (white) powder and peppermint oil. A study by Van Den Akker et al. found that patients who reacted to colophonium, balsam of Peru or fragrance mix had significantly more reactions to nutmeg, paprika and cloves when compared to patients who did not react to colophonium, balsam of Peru or fragrance mix. Fragrance mix was the most important indicator allergen for these three spices.[44]

4.2 | Irritant contact dermatitis

Despite the prevalence of vICD, we could merely include two studies on vICD,[22,26] which presumably results from the lack of specific diagnostic tests.[5,45] Farage proposed the use of the Behind-the-knee (BTK) test on that account and found that the popliteal fossa better reflected mechanical and chemical skin irritation of the vulva compared to standard patch testing on the arm.[46]

4.3 | Patch testing

Patch testing is an important tool in diagnosing vACD. However, the adequacy of this method could not be determined. Of the studies that specifically mentioned the application site, the upper back was used as the conventional place to apply the patches.[13,17,23] While it could be argued that the upper back is not representative for the vulvar skin, patch testing on the skin of the labia is practically inconvenient. The area is relatively small, exposed to multiple secretions possibly leading to bad adherence of the patches and testing on the labia can be a source of discomfort for the patient.

Batchelor et al. found that only using the EECDRG series would have missed 31.1% of positive results.[15] This illustrates the importance of broadening the test spectrum with other products such as personal products, extended and specialized series, common over the counter products, etc. Recommendations for the addition of allergens to the European baseline series have been made by Wilkinson et al.[47] Recommended allergens that were also identified in this systematic review are: sodium metabisulphite, 2-bromo-2-nitropropane-1,3-diol, diazolidinyl urea, imidazolidinyl urea and compositae mix II.

Concerning the duration of patch testing, some studies performed an additional reading at day 6 or 7 to identify late corticosteroid reactions.[13,16,17,19] This is in line with the findings of Van Amerongen et al., who found that 13.5% of contact allergies would have been missed when no reading was performed on day 7. Topical drugs (corticosteroids not included) and corticosteroids were the two groups that gave the most late positive reactions, 33.3% and 28.4%, respectively. The individual allergen with the highest proportion of new positive reactions was neomycin sulphate (81.5% of total). These findings suggest a need for readings at day 7 to identify late reactions that could otherwise go undetected.[48]

4.4 | Limitations

This systematic review has several limitations. Firstly, 16 of the 17 included studies had a cross-sectional study design. Nine studies had a retrospective design, which could lead to data incompleteness and data collection problems. Secondly, studies were performed in secondary and tertiary centres, often only accessible via referral, and hence, presumably involved highly selected study groups/populations. Thirdly, there was heterogeneity across the studies concerning the presentation of the results and the patch testing techniques. Some studies only reported relevant positive reactions and other studies did not mention relevance at all. Separate data for men and women was not available in every study. Some studies discussed strictly genital involvement, while other studies discussed the anogenital region. For these reasons, interpretation can be difficult. Furthermore, basic demographic data were often missing. Only three studies mentioned ethnicity and the differentiation between pre- or post-menopausal was not always made. Lastly, this systematic review only included two studies concerning vICD.

5 | CONCLUSIONS

In conclusion, this systematic literature research revealed a variety of potential allergens involved in vACD, although some hapten classes and particular allergens tend to be more common in the published data. In order to identify the sensitizing culprits, additional series as well as the products used by the patients, along with the ingredients, should be patch tested. Studies on vICD are scarce and further research is necessary.

AUTHOR CONTRIBUTIONS

Sander Vandeweege: Conceptualization; investigation; writing – original draft; methodology; visualization; validation; formal analysis; project administration; data curation. **Britt Debaene:** Conceptualization; investigation; writing – original draft; methodology; validation; visualization; formal analysis; project administration; data curation. **Hilde Lapeere:** Validation. **Hans Verstraelen:** Conceptualization; supervision; project administration; validation.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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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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