Review Article

Vulvar Pruritus—Causes, Diagnosis and Therapeutic Approach

Linn Woelber, Katharina Prieske, Werner Mendling, Barbara Schmalfeldt, Hans-Jürgen Tietz, Anna Jaeger

Summary

Background: In Germany, 17–23% of the population suffers from chronic itching of the skin; in 5–10% of cases, the female genitalia are affected, specifically, the vulva. Vulvar pruritus is thus a common symptom that often markedly impairs the affected women's quality of life.

Methods: This review is based on pertinent publications that were retrieved by a selective search in MEDLINE/PubMed for articles on the pathogenesis, diagnosis, and treatment of vulvar pruritus. The search terms were (in German and English) “vulvärer Juckreiz,” “pruritus vulvae,” and “genital itch,” alone and in combination with “Behandlung,” “Therapie,” or “treatment.”

Results: The most common cause of vulvar pruritus is vulvo-vaginal candidiasis followed by chronic dermatoses, such as lichen sclerosus and vulvar eczema. Especially in refractory cases, an invasive or preinvasive lesion such as squamous epithelial dysplasia (VIN, vulvar intraepithelial neoplasia) should be borne in mind in the differential diagnosis. Rarer causes include infection, atrophy, and vulvodynia. The essential elements of treatment are topical/oral antimycotic drugs and high-potency glucocorticoids, along with consistently applied, basic moisturizing care and the avoidance of potential triggering factors.

Conclusion: As vulvar pruritus has multiple causes, standardization of its diagnostic evaluation and treatment would be desirable, both to achieve optimal efficacy and to meet the diverse needs of women who suffer from this condition.

Cite this as:

Wölber L, Prieske K, Mendling W, Schmalfeldt B, Tietz HJ, Jaeger A: Vulvar pruritus—causes, diagnosis and therapeutic approach. *Dtsch Arztebl Int* 2020; 117: 126–33. DOI: 10.3238/arztebl.2020.0126

In Germany, 17% to 23% of the population suffer from chronic (≥ 6 weeks) pruritus of the skin (1, 2). In 5% to 10% of cases, the female genitalia—and in particular the vulva—are affected (3–6). Thus, vulvar pruritus is a common symptom which often significantly impairs the patient's quality of life. The underlying pathophysiological mechanisms are not yet fully understood. In the past, itching was generally considered to be a subtype of pain sensations. Today, however, it is assumed that it is an independent sensory quality mediated by free nerve endings of unmyelinated C-fibers. These nerve endings respond to chemical, mechanical and thermal stimulation and are activated by specific mediators, such as kinins, prostaglandins, and neuropeptides (7, 8).

In patients experiencing genital itching, the medical history should be taken in a systematic manner (*Figure 1*), covering the following aspects:

- Symptom duration (acute/chronic)
- Localization (local/generalized)
- Intensity (scale 1–10)
- Pre-existing systemic disorders (e.g. autoimmune disease/diabetes mellitus)
- Ameliorating/aggravating modulators
- Previous treatments.

Since the skin in the genital area is influenced by sex hormones, the question whether hormonal medications, such as contraceptives, are taken is also an important part of the clinical history.

The, at times, complex ties between the various causal factors involved in the pathophysiology of vulvar pruritus (*Figure 2*) can often be satisfactorily evaluated by inspection, speculum examination and microscopy of vaginal discharge.

During the inspection of the external genitalia, attention should be paid to superficial skin changes, such as erosions or plaques. Besides discolorations and abnormalities of the skin markings, the margins and configurations of the lesions noted should also be taken into account. The classification of the International Society for the Study of Vulvovaginal Disease (www.issvd.org) is a tool to categorize the morphological (shape/form) features which has been shown to be particularly useful. Using this classification system, the range of potential differential diagnoses can be narrowed down.

In patients with refractory candidiasis/infection, microbiological swap tests, culture-based tests, and

Department of Gynecology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany: Prof. Dr. med. Linn Woelber, Dr. med. Katharina Prieske, Prof. Dr. med. Barbara Schmalfeldt, Dr. med. Anna Jaeger

German Center for Infections in Gynecology and Obstetrics, Wuppertal, Germany: Prof. Dr. med. Werner Mendling

Institute of Fungal Disease and Internal Medicine, Mycoclinc Berlin, Berlin, Germany: Prof. Dr. med. Hans-Jürgen Tietz

FIGURE 1

Differential diagnostic work-up and diagnosis of vulvar pruritus by morphology (nomenclature see Box); bact., bacterial; surg., surgical; ultrapotent, ultrapotent; GC, glucocorticoids; Inf., infection; mechan., mechanical; NAAT, nucleic acid amplification test; p.o., per os; VIN, vulvar intraepithelial neoplasia

FIGURE 2

Common differential diagnoses of vulvar pruritus

amplification techniques may be needed to confirm the diagnosis. For a more detailed assessment of the vulva, it is recommended to perform a vulvoscopy as this allows to exam the skin of the vulva under 7x to 30x magnification. 5% acetic acid is applied to aid visualization of suspicious areas. Findings suspicious of vulvar intraepithelial neoplasia (VIN)/invasive lesions as well as unclear or refractory vulvar skin changes are indications for a 4–6 mm punch biopsy which can usually be performed without difficulty under local anesthesia. In addition to the examination of the vulva, inspection of both groins, the anal fold and, in some cases, the entire integument is indicated as it may yield important clues about the underlying cause of the clinical signs and symptoms.

The aim of this article is to develop algorithms for the diagnosis and treatment of pruritus, on the basis of signs, symptoms and morphological features, which are suitable for use in clinical practice. In addition, clinically relevant parameters of the most common conditions associated with vulvar pruritus will be discussed.

Methods

A search of the literature was conducted in the MEDLINE/PubMed database without publication date limits. Publications on the etiology, diagnosis and treatment of vulvar pruritus were included. The following search terms were used: “vulvärer Juckreiz“, “pruritus vulvae“, “genital itch“, alone and in combination with “Behandlung“, “Therapie“, “treatment“. The level (or quality) of evidence (LoE) is reported using the GRADE approach (9).

Common differential diagnoses of vulvar pruritus

The most important conditions associated with vulvar pruritus are presented in *Figure 2*. The respective clinical presentation, characteristic morphological features and the diagnostic approach, as well as the recommended specific treatment are shown in *Figure 1* and the *eFigure*. The *Table* provides a detailed description of the most important conditions. In addition, three current topics of increasing importance in the future will be discussed in detail:

- Candida glabrata infections
- The role of the vaginal microbiome
- Genetic polymorphism in lichen sclerosus (LS).

Treatment of vulvar pruritus

As a rule, continuous basic care has a positive effect on the course of treatment in patients with vulvar itch. Basic care includes avoidance of potential trigger and provocation factors, such as fragrances, cleaning products with emulsifiers or antimicrobial agents (e.g. parabens), latex-containing condoms, as well as lubricants and preservatives. Apart from that, lipid-replenishing, breathable topical preparations should regularly be used to support the barrier function of the vulvovaginal skin/mucosa (10–12). For this purpose, ointments with high fat content are especially useful and should be given preference over creams which contain the above mentioned additional ingredients.

Other recommendations include to refrain from wearing (too) tight clothing and shaving the pubic hair and to use silk or cotton underwear (13–16). A study including 96 women with recurrent vulvovaginal candidiasis (VVC) (median age: 30 years) found that wearing silk underwear while continuing oral treatment with 150 mg fluconazole once weekly significantly reduced vulvar itching ($p < 0.0001$) and burning ($p < 0.005$) compared to the control group (16). A randomized trial including 42 women with lichen sclerosus (median age: 51.5 years) treated with clobetasol 0.05% (13) arrived at similar results: In addition to improvements in clinical symptoms, such as burning, skin irritation and pain ($p < 0.0001$), faster relief of itching was observed in the group of patients wearing silk underwear compared to the control group ($p < 0.005$).

Disease-specific treatment approaches are shown in *Figure 1* and in the *Table*. Due to the, at times, complex pathogenesis of the condition, an interdisciplinary treatment strategy may be required to achieve

TABLE

Characteristic conditions*

	Candidiasis	Lichen sclerosus	Lichen planus	VIN (vulvar intraepithelial neoplasia)	Eczema	Psoriasis
Clinical presentation
Frequency (prevalence)	10–20%	0.1–3%	0.1–0.8%	Exact prevalence unknown, incidence approx. 3/100 000 women in Germany	0.5–10%	2%
Morphological features	Red and white plaques, erosions, ulcers	– Early form: erythema, erosions – Late form: white, firm plaques, bleeding into skin, scarring, atrophy, fissures, exaggerated skin markings	– Early form: character. whitish reticulate (Wickham) striae – Late form: erosive erythema, scarring, extragenital involvement (e.g. oral)	– Early form: pruritus, burning, soreness, often asymptomatic – Late form: dyspareunia, burning, vaginal stenosis	– Poorly marginated erythematous lesions on the labia majora and labia minora, edema (acute), lichenification (chronic)	– Well-demarcated, slightly scaly, erythematous red plaques, accompanying fissures and rhagades
Signs & symptoms	Pruritus, erythema, increased vaginal discharge (white, curd-like, no odor)	Pruritus, burning, dyspareunia	– Early form: pruritus, burning, pain – Late form: dyspareunia, burning, vaginal stenosis	Pruritus, burning, soreness, often asymptomatic	Pruritus, soreness	Pruritus
Diagnosis	pH value: normal (< 4.0) Lactobacilli: yes Leukocytes: increased Clue cells: none Microscopy: Pseudomycelium & blastospores	History, clinical examination, typical figure-of-8 pattern surrounding the vulva and anus; histological confirmation by biopsy, if required	History, clinical examination, characteristic Wickham striae, vaginal involvement; histological confirmation by biopsy	Vulvoscopy, histological confirmation by biopsy	History, clinical examination; if necessary, patch test	Typical involvement of labia majora, characteristic non-involvement of labia minora
Management	– Acute: Antifungal agent (e.g. oral fluconazole or topical clotrimazole preparations) – Chronic: Following the initial treatment, fluconazole 150 mg orally 1 x/week for at least 6 months after loading dose	– Initially ultrapotent glucocorticoids (GC) (topical) – Life-long GC maintenance dose in reduced dose, lipid replenishment – Second-line therapy: calcineurin inhibitors (off-label)	– Initially ultrapotent glucocorticoids (GC) (topical) – Life-long GC maintenance dose in reduced dose, lipid replenishment – Second-line therapy: calcineurin inhibitors (off-label)	– Laser vaporization (standard with usual-type VIN) – Surgical excision rather with differentiated VIN (Warning: occult carcinoma) – Imiquimod 5%, topical for usual-type VIN (off-label)	– Avoidance of trigger factors – Glucocorticoids (topical)	– Avoidance of mechanical stress and trigger factors – Topical treatment as for extragenital psoriasis (typically GC/calcineurin inhibitors)

Compiled based on (e41–e45); VIN, vulvar intraepithelial neoplasia

* Photographs courtesy of Prof. Dr. Linn Woelber and Prof. Dr. Werner Mendling

favorable long-term results. Obtaining a biopsy is critical to ensure that in patients with refractory lesions possible (pre-) invasive changes are ruled out. These include, among others, (see *Box*):

- Hyperkeratotic lesions which cannot be wiped off
- Leukoplakia
- Fissures
- Erosions
- Ulcers

This also applies to patients where the pathogenesis of the vulvar pruritus has remained unclear and a histopathological diagnosis could inform subsequent treatment. In both cases—presence of (pre-) invasive lesions and also inconclusive vulvar examination findings—these patients should be referred to a specialized outpatient clinic to ensure speedy initiation of an effective treatment.

In patients with persistent, idiopathic vulvar pruritus, as a rule the following treatment option should be considered:

- Local cooling
- Evening dosing of an antihistamine, e.g. hydroxyzine (10, 17)
- Anticonvulsants, in the form of gabapentin (2)
- Antidepressants, such as doxepin, sertraline, mirtazapine (2, 18, 19)
- Opioid antagonists, e.g. naltrexone (20)
- Transcutaneous electrical nerve stimulation (TENS) (21)
- Acupuncture (22).

Furthermore, it is crucial to ask questions regarding potential psychosocial and psychosexual causes and, if any, to address these in collaboration with psychologists, psychotherapists and specialists in sexual medicine.

Vulvovaginal candidiasis

Genital candidiasis is a common infection and a primary cause of vulvar pruritus, accounting for 35% to 40% of cases (23). The most common pathogens are *Candida albicans* (>90%) and *Candida glabrata* (approx. 2%). 75% of women will have at least one episode of VVC during their lifetime and about 8% will have chronic VVC (at least 4 recurrences/year) (24–29). Treatment recommendations for acute/chronic VVC are shown in *Figure 1* and the *Table*. Below, individual aspects with relevance for clinical practice will be discussed in greater detail.

Compared to *C. albicans*-induced VVC, the clinical signs and symptoms of *C. glabrata*-induced VVC are generally milder. Other characteristic features of *C. glabrata*-induced VVC include absence of leukocytosis and pseudomycelium formation in the wet preparation as well as production of less vaginal discharge (30). The recommended treatment for *C. glabrata*-induced VVC is still an oral dose of 800 mg fluconazole for 2 to 3 weeks (level of evidence II; grade of recommendation: C) (25). Given the rapid development of resistance in recent years, which is primarily attributable to the genetic variability

of the pathogen at doses of less than 800 mg fluconazole, satisfactory long-term treatment has increasingly become a challenge (31–33). Today, fluconazole-sensitive strains are only occasionally encountered in clinical practice and the remaining strains cannot be treated with the triazole derivatives voriconazole or posaconazole either, because of additional cross-resistances. For this reason, it is necessary to use echinocandins for the systemic treatment of *C. glabrata*, a new class of antifungal agents which includes, besides caspofungin and anidulafungin, also micafungin, the currently preferred agent (30).

In a randomized controlled trial with 531 patients with invasive candidiasis, micafungin (100 mg/day or 2 mg/kg body weight [BW]/day) was as effective (89.6% success rate in both groups) as liposomal amphotericin B (L-AmB) (3 mg/kg BW), but caused fewer adverse events (34). While echinocandin class antifungal agents have been available for the treatment of esophageal and invasive candidiasis and other indications since the approval by the US Food and Drug Administration (FDA) in 2001 (35), no high-quality study data have yet become available to support their use in the treatment of chronic recurrent VVC. For this reason, micafungin, an expensive drug which is given intravenously, has not been approved for the treatment of vaginal mycosis, even though it has been shown to be highly effective against *C. glabrata* (36). First promising treatment concepts favor a systemic treatment approach consisting of a 15-day treatment with 150 mg micafungin intravenously/day in combination with ciclopirox olamine cream and nystatin vaginal ovules (30). Treatment strategies commonly recommended in other countries, such as boric acid vaginal suppositories (600 mg) or flucytosine 17%, are not available in Germany. However, because of their increased toxicity, their use is also not recommended (25, 37).

The importance of the human vaginal microbiome—i.e. the totality of all microorganisms present on the vaginal mucosa—in the pathogenesis of vulvar pruritus, especially if the itching is caused by chronic recurrent fungal infections, remains the subject of controversy in the current literature. Compared to the intestinal and oral microbiota, the vaginal microbiome shows less diversity, with 100 to 200 different species (38). The range of species changes several times over the course of a lifetime due to variations in hormone levels. The composition of the vaginal microbiome is influenced by genetic factors, among others, and shows ethnic differences. In more than 70% of cases, the natural colonization of the vagina is dominated by lactobacilli (primarily *L. crispatus*, *L. gasseri*, *L. jensenii*, and *L. iners*) (39, 40). By acidifying the vagina and producing antimicrobial substances, such as lactic acid and hydrogen peroxide, lactobacilli protect against the adhesion of facultative pathogens (e1).

BOX

Nomenclature of vulvar changes (morphology) according to the International Federation for Cervical Pathology and Colposcopy (IFCPC)

● Definitions of primary lesion types

Macule	= small (<1.5 cm) discolored, flat, non-palpable area
Patch	= large (>1.5 cm) discolored, flat, non-palpable area
Papule	= small (<1.5 cm) elevated and palpable lesion
Plaque	= large (>1.5 cm) elevated, palpable and flat-topped lesion
Nodule	= large papule (>1.5 cm), often hemispherical or poorly demarcated; on the surface; cystic or solid lesion
Vesicle	= small (<0.5 cm) blister containing clear fluid
Bulla	= large (>0.5 cm) blister containing clear fluid
Pustule	= pus-filled blister; content is white or yellow

● Definitions of secondary morphology presentation

(develops from the primary lesion by proliferative transformation, regression or healing)

Eczema	= Inflammatory, non-infectious intolerance reaction characterized by the presence of itchy, poorly demarcated red plaques with minor evidence of microvasculature and/or (more frequently) subsequent surface disruption
Lichenification	= Thickening of the tissue and increased prominence of skin markings, with or without scaling, bright red, dusky red, white or skin-colored.
Excoriation	= Substance defect of the skin extending into the dermis (often scratch marks)
Purpura	= Multiple smaller capillary hemorrhages in the skin, subcutis or mucosa
Scarring	= Replacement tissue after wound healing; often white, fibrous, poorly vascularized
Erosion	= A shallow defect in the skin/mucosa with absence of epidermis/epithelium; the dermis is intact
Fissure	= A thin, linear erosion of the skin/mucosa
Ulcer	= Deeper defect of the skin; absence of the epidermis and some, or all, of the dermis

● Suspicion of neoplasia

Gross neoplasia, ulcer, necrosis, hemorrhage, exophytic lesion, hyperkeratosis with/without white, gray, reddish brown discoloration

Since 2008, research on the microorganisms inhabiting the human body has been carried out by the Human Microbiome Project and the Vaginal Microbiome Project of the National Institute of Health (NIH) (38). While more recent studies have demonstrated a causal relationship between changes in the composition of the vaginal microbiota and an increased risk of infection (e2–e5), no significant difference was found in a study comparing the dominant *Lactobacillus* species in women with VVC and without VVC (e6). Despite the lack of convincing long-term data regarding the therapeutic targets, it appears that the use of probiotics reduces the VVC recurrence rate (e1, e7–e9). For example, in first clinical studies women with chronic recurrent VVC were treated with 250g yoghurt containing *L. acidophilus* over a period of 6 months. The number of new vulvo-vaginal *Candida* infections was 2.5 in the control arm versus 0.38 in the treatment arm ($p = 0.001$) (e9, e10). Preparation of wet-mount slides continues to be the

most important diagnostic test to differentiate between normal and abnormal composition of the vaginal microbiome. It is supplemented by a microbiological culture. In addition, modern sequencing techniques, such as next-generation sequencing (NGS), allow for a much more differentiated interpretation and have the potential to become the foundation of our future understanding of the genital tract's colonization by a wide variety of species of microorganisms.

In Germany, patients with recurrent episodes of vaginitis and VVC are sometimes offered immunization with inactivated lactobacilli of various species. The aim of this immunization is to induce specific antibodies against aberrant strains in the Döderlein's flora which do not contribute to the normal vaginal milieu. At the same time, this treatment aims to achieve regeneration of the affected vaginal flora and restoration of the normal vaginal pH and consequently a general enhancement of local vaginal

Key messages

- Vulvar pruritus is an often complex symptom of multifactorial etiology. Its diagnosis and treatment requires an interdisciplinary approach, involving gynecologists, dermatologists, microbiologists, infectiologists, psychotherapists, physiotherapists, and, potentially, specialists in sexual medicine.
- The most common cause of vulvar pruritus is vulvovaginal candidiasis followed by vulvar eczema and chronic dermatoses, such as lichen sclerosis.
- 75% of women will have at least one episode of vulvovaginal candidiasis during their lifetime and 6% to 8% will have chronic vulvovaginal candidiasis (at least 4 recurrences/year).
- Vulvar skin changes, such as erosions, ulcers or hyperkeratotic lesions, which are refractory to treatment, require histological diagnosis, which is obtained by punch biopsy. Vulvar cytology has very low specificity and does not provide acceptably reliable results.

immunity (e11). The recommended regimen consists of basic immunization with 3 doses at 2-week intervals and a booster dose after 6 to 12 months. The primary indication is bacterial vaginosis. The available studies showed a significant reduction in recurrence rate by up to 80% (e12–e14). Taking into account cross-protection mechanisms, therapeutic benefits are also expected in patients with VVC. However, based on the available data on the use of this approach in patients with VVC, the benefit of immunization treatment for this condition is still uncertain. Thus, it should only be used in addition to antifungal treatment.

Lichen sclerosis

LS is the most common dermatosis of the vulva associated with itching. It often takes a relapsing chronic course and is considered to be a facultative precancerous condition which can develop into squamous cell carcinoma (e15). The etiology of LS is still not fully understood. Currently, a multifactorial etiology is assumed, primarily driven by genetic and immunological factors. Evidence in support of genetic causes of LS include familial aggregation in up to 17% of cases (e16–e18), significant correlation of LS with Human Leucocyte Antigen (HLA)-A28 or HLA-B44 (e19) and the presence of HLA-DQ7 in 66% of the affected women (e20, e21).

In addition to the immunological aspects of LS pathogenesis, which appears to involve a local cell-mediated dermal response to an antigen which has not

yet been identified with certainty (e22), a preponderance of cytotoxic CD8⁺ and CD57⁺ lymphocytes was found in the inflammatory cells present in lichenoid lesions—similar to the proliferation of CD8⁺ and CD57⁺ lymphocytes in chronic antigen-mediated inflammatory reactions (e23). Furthermore, 15% to 34% of patients with LS have T-cell-mediated autoimmune diseases, such as Hashimoto's thyroiditis (12%), alopecia areata (9%) and vitiligo (6%) (e24–e26).

In a study with 350 LS patients, 21.5% of patients had one or more autoimmune diseases, 21% had a family history of autoimmune disease and 42% had autoantibodies in titers of >1:20 (e26). The assumption of an autoimmune pathogenesis of LS is also supported by data from an English study which detected IgG autoantibodies to extracellular matrix protein-1 (ECM1) in the serum of 67% of patients compared to 7% in the control group (e27). Nevertheless, the existence of an LS-specific antibody cannot be concluded from these study results. The identified antibodies to extracellular matrix proteins are more likely a phenomenon secondary to tissue destruction (e28). Further studies found autoantibodies to the basal membrane proteins BP180 and BP320 (e29, e30) and thyroid autoantibodies in 30% to 80% and 9% of patients, respectively (e24). Even though the precise mechanisms underlying the synthesis of these antibodies are not fully understood, these results indicate that LS is caused by a humoral autoimmune reaction (e31).

In addition, infections with *Borrelia burgdorferi* (e32), human papillomavirus (HPV) (e33) and Epstein-Barr-Virus (e34), as well as local effects, such as Koebner phenomenon, are being discussed as possible causes of LS (e35).

Application of ultrapotent topical corticosteroids, such as clobetasol 0.05% ointment for initially 3 months, remains the first-line treatment for genital LS (LoE Ib, A) (e15, e36, e37). This should usually be followed by life-long reduced-dose maintenance therapy (LoE Ib, A). Both the therapeutic effectiveness and the cancer risk-reducing effect of corticosteroids have repeatedly demonstrated been in various studies (e38, e39). In refractory patients, an off-label treatment attempt with calcineurin inhibitors, such as 1% pimecrolimus and 0.03%/0.1% tacrolimus, can be made (LoE Ib, A) (e40).

Conclusion for clinical practice

Vulvar pruritus is a complex symptom of multifactorial origin, frequently affecting the patient's quality of life. The treatment of patients with chronic pruritus (>6 weeks) is particularly challenging and often requires a multimodal strategy with an interdisciplinary approach. Besides the elimination of potential triggers and continuous lipid-replenishing basic care, antifungal agents and glucocorticoids are paramount. Medical professionals not specialized in the field should refer patients with refractory and/or suspicious lesions to an

experienced gynecologist. A specimen should be obtained by punch biopsy for histological evaluation to rule out (pre-) malignant lesions.

It is central to the management of vulvar pruritus to offer a detailed discussion of the condition and treat patients with empathy. Their complaints should be taken seriously and patients should be informed about what could cause their symptoms and which treatment options are available for them.

Conflict of interest

Prof. Woelber received authorship/co-authorship fees for a publication related to the topic from Springer Verlag and Thieme-Verlag. She received congress fees and reimbursement of travel expenses as well as lecture fees from med update GmbH, medac oncology, Jörg Eickeler, promedicis GmbH, AG-CPC, Roche, Tesaro, TEVA, OmniaMed, and AGO research GmbH. She received study support (third-party funding) from Greiner, Roche Diagnostics and medac oncology.

Dr. Prieske received reimbursement of travel expenses and lecture fees from medac oncology and Jörg Eickeler.

Prof. Mendling received congress fees and reimbursement of travel expenses as well as lecture fees from Dr. Kade GmbH.

Prof. Schmalfeldt received lecture fees from promedicis GmbH.

Prof. Tietz received reimbursement of travel expenses and lecture fees from Bayer Leverkusen.

Dr. Jaeger declares no conflict of interest.

Manuscript received on 16 May 2019, revised version accepted on 27 November 2019

Translated from the original German by Ralf Thoene, MD.

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Corresponding author

Prof. Dr. med. Linn Woelber
Klinik und Poliklinik für Gynäkologie
Universitätsklinikum Hamburg-Eppendorf
Martinistraße 52, 20246 Hamburg, Germany
lwoelber@uke.de

Cite this as:

Woelber L, Prieske K, Mendling W, Schmalfeldt B, Tietz HJ, Jaeger A: Vulvar pruritus—causes, diagnosis and therapeutic approach. Dtsch Arztebl Int 2020; 117: 126–33. DOI: 10.3238/arztebl.2020.0126

► Supplementary material

For eReferences please refer to:
www.aerzteblatt-international.de/ref0820

eFigure:
www.aerzteblatt-international.de/20m0126

Supplementary material to:

Vulvar Pruritus—Causes, Diagnosis and Therapeutic Approach

by Linn Woelber, Katharina Prieske, Werner Mendling, Barbara Schmalfeldt, Hans-Jürgen Tietz, and Anna Jaeger

Dtsch Arztebl Int 2020; 117: 126–33. DOI: 10.3238/arztebl.2020.0126

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eFIGURE

Differential diagnostic work-up and diagnosis of vulvar pruritus by symptom (according to Stockdale Obstet Gynecol 2018 [e46]); VIN, vulvar intraepithelial neoplasia