Review article

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Allergic vulvovaginitis

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Learning objectives: The reader of this review will learn about the different clinical forms of allergic vulvovaginitis. This specific and important chapter has not been previously summarized and described in the medical literature. Vaginal mucosa is also able to show an allergic response similarly to the nose, eyes, lungs, and skin. Physicians should be familiarized with this kind of manifestation in order to make the proper diagnosis and evaluation of this entity.

Data sources: MEDLINE searches were undertaken since 1966 for citations of any kind of allergic vulvovaginitis. Relevant reviews and articles identified in this process were surveyed for additional and earlier citations. Textbooks of medicine, gynecology, dermatology, and infectious diseases have also been consulted. Old medical textbooks and journals of allergy and internal medicine were recovered from the Division of History of the Medicine of the Faculdade de Medicina da Universidade Federal de Minas Gerais (Federal Medical College), Belo Horizonte, Brazil.

Conclusions: A great variety of allergens are able to provoke allergic reactions in the female genital tract. The immunology of the vagina, the influence of hormones, menstrual cycle, and psychologic factors are also highlighted in this review. A possibility of vaginal hyperreactivity is proposed in this text. Adequate management provides important relief of symptoms in the majority of cases.

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INTRODUCTION

Recent studies on allergen challenge in the nose, eyes, lungs, and skin have shown that the typical immediate reaction (early phase) is usually followed by a late inflammatory reaction phase causing subsequent symptoms. This has led to the current view of a complex inflammatory network common to various allergic diseases and the final clinical picture depends on the target site where allergens interact with the immune cells. Allergists should regard allergic vulvovaginitis as a major issue, along with cultivating a more unified approach to the allergic patient.[1] In spite of the lack of provocation vaginal studies, clinical manifestations of allergic vaginitis is sometimes part of the work of a practicing allergist.[2] Vaginal mucosa is also able to show an allergic response similarly to the nose, eyes, lungs, and skin, thus allergists should include this organ in the network of allergic diseases.

A specific allergic response in the vagina can be elicited in several ways. In atopic women, no immunophysiologic reason was found that could exclude chemical mediators being released in the genital tract. On the other hand, vulva and vagina may be important routes for the entrance of allergens that induce local or even severe systemic reactions.[2,3]

Since the beginning of the 20th century, some allergists have occasionally focused on such manifestations.[4,5] A recent review article on vulvovaginitis reports the allergy as an important cause.[6] Seminal fluid components, medications taken by the partner and present in his semen, spermicides, soaps, sanitary napkins, latex, intestinal parasites, and *Candida albicans* may induce immediate hypersensitivity reactions. In addition, allergens such as pollen, dust, or food particles can be inadvertently introduced into the vagina by the fingers or even systemically absorbed.

IMMUNOLOGY OF THE VAGINA

Vaginal protective mechanisms against pathogens include mucosal secretory immunity, cyclic menses, bioactive reproductive secretions, low pH, and metabolic products from commensal organisms. Knowledge of the human vagina ultrastructure derives mainly from a study published in 1978.[7] The vaginal epithelium is composed of five distinct cell layers. From the vaginal lumen, the first three layers are named superficial, transitional and intermediate, respectively. Each one is composed of approximately 10 rows of squamous epithelial cells. Beneath these layers are the parabasal and basal layers, containing one to two rows of columnar epithelial cells. The basal lamina (basement membrane) underlies the basal epithelia.

Traversing the vaginal epithelia there is a system of intercellular channels, which provides a mechanism for macromolecules, fluids, and cells to migrate from the vaginal basal lamina to the vaginal lumen or vice versa.

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The human vaginal basal lamina contains macrophages, Langerhan's cells, eosinophils, lymphocytes, plasma cells, and mast cells. Macrophages and Langerhan's cells, lymphocytes, migrate into the interepithelial channels. The presence of IgG- and IgA-producing plasma cells and lymphocytes in the basal lamina associated to an accessible pathway to the lumen, strongly suggests that the vagina may be able to mount a mucosal immune response.[8]

Langerhan's cells are bone marrow-derived macrophage-like dendritic cells that accumulate at sites of inflammation. They express cell surface receptors for the constant region of the IgG (FcγR) and for complement C3, and class II major histocompatibility complex antigens (HLA-DR) are also present on the surface of Langerhan's cells; therefore, Langerhan's cells are able to present antigens to T lymphocytes and initiate a specific immune response.[8]

A number of studies have shown that vaginal immune response causes some cases of recurrent vaginitis. IgE antibodies to *C. albicans*, seminal fluid components, pollen, and contraceptive spermicides have been identified in vaginal fluids of women with recurrent vaginitis.[9] In many instances, presence of prostaglandin E_2 in the vagina and detection of eosinophils in vaginal smears were also observed.[10]

Exposure to allergen in the vaginal lumen is followed by the transport of this allergen through the interepithelial channels and its interaction with mast cell-bound specific IgE. This induces mast cells degranulation and the release of histamine and other inflammatory mediators, causing symptoms of allergic vaginitis. In addition, histamine is a potent inducer of prostaglandin E_2 from macrophages which suppresses cell-mediated immune response. Unlike bacterial infections, in which humoral immunity is an important component of defense, protection against yeast is dependent on the cellular immune system. The resulting symptomatic candidal vaginitis would be a secondary consequence to a primary allergic vaginitis.[9]

ACCUMULATION AND ABSORPTION OF BIOACTIVE SUBSTANCES FROM THE VAGINAL LUMEN–VAGINAL HYPERREACTIVITY

The human vaginal mucosa has some particularities with regard to the blood flow that may influence the concentration of various substances that probably facilitate the development of local and systemic allergies.

Early studies found that peanut protein placed in the human vagina could be detected in the circulation after 1 to 2 hours.[11] The ability of intravaginal penicillin, steroids hormones, seminal fluid, and prostaglandins to be absorbed systemically has also been recognized for many years.

In 1990, Sjoberg et al[12] demonstrated that in healthy women penicillin reached maximum levels in the serum and saliva 1.5 hours after oral ingestion of a single tablet and was undetectable at these fluids by 15 hours. By contrast, the penicillin concentration in the vagina of these women continually increased over a 15-hour period. This suggested that orally ingested compounds may accumulate in the vagina. A mechanism to explain this situation was provided in an early study,[13] that identified a countercurrent blood flow in the female genital tract.

The physiologic features that allow a selective accumulation of allergens in the vaginal lumen, their passage through the interepithelium channels, and the subsequent binding to specific IgE on mast cells in the subepithelium basal lamina could explain the newly characterized occurrences of allergic vaginitis.[8] The routes of vaginal sensitization would be by direct or indirect contact with hands, fingers, or clothes,[14] sexual intercourse,[2] and after ingestion, including food and drugs ingested by the male partner[15] or inhalation.[16]

It is also likely that, as in other target organs of the allergy, a nonspecific vaginal hyperreactivity[17] may be present in some cases, and vaginitis may be induced by many types of nonallergic triggering factors.[17,65] An ethical and objective parameter to measure this clinical hyperresponsiveness is still needed.

MENSTRUAL CYCLE, HORMONES, AND VAGINAL IMMUNE RESPONSE

Undoubtedly, there is a clear relationship between the endocrine and the immune system. Hormone secretion is influenced by immunologic factors and vice-versa. Regulation of mucosal immunity in the female reproductive tract through the reproductive cycle is well established. Endocrine changes regulate the levels of IgA and IgG in uterine and vaginal secretions.[18] As expected, the vaginal epithelium, interepithelial channels, and lymphoid cell concentration are all influenced by the menstrual cycle, which can be divided into four phases: (1) menstruation, (2) preovulatory phase (proliferative), with a predominance of estrogen, (3) periovulatory phase, when both estrogen and progesterone are active, and (4) postovulatory phase (lutheal), with a predominance of progesterone which remains until the next menstruation.

Estrogen-induced mitosis in the basal and parabasal layers is maximal during the proliferative phase and results in epithelial thickening. Conversely, under the influence of progesterone, interepithelial channels become atrophic during the ovulation and the lutheal phase of the cycle.[19]

Immunosuppressive effects of vaginal lavage fluids collected during menstruation and in the periovulatory phase may indicate an attenuation of normal immune surveillance and enhanced susceptibility to infections and allergic reaction during these periods. Immunosuppression during the periovulatory phase may also be a mechanism for attenuation of a woman's immune response to spermatozoa.[19]

It has also been demonstrated in mice that the vagina is an inductive site for mucosal immune response. Reduced antigen presentation occurs at a time in the reproductive cycle that coincides with ovulation and the intravaginal deposition of sperm.[18]

Some studies show that progesterone favors the development of T-helper cells producing Th2 type cytokines which are responsible for the IgE-mediated hypersensitivity reactions.[20,21] The immune response to *C. albicans* and therefore the ability of this organism to proliferate and undergo the asymptomatic yeast to-germ tube transition is influenced by high levels of progesterone.[22] This explains the fact that the incidence of allergic reactions and candidal vaginitis is most common in the late lutheal phase, just prior to menstruation.[6,8,18,21]

SPECIFIC ALLERGIC REACTIONS AFFECTING THE VULVA AND VAGINA

Inhalants

At least eight publications from 1920 to 1995 describe allergic vulvovaginitis due to pollens.[4,5,14,23–27] In 1998, Moraes reported a case of a child with perennial nasal and vaginal symptoms due to house dust mite.[28] In 1999, Chiu et al reported an adult woman suffering from allergic vaginitis due to inhaled latex.[16] In these cases, an increased number of eosinophils in the vaginal smear, positive immediate skin tests and/or RAST to pollen, house dust mite and/or latex were observed as well as association with other allergies and family history of allergy.

We may hypothesize that besides direct contact, allergens could be systemically absorbed after inhalation. This kind of sensitization has recently been demonstrated in a double-blind provocation test in patients with atopic dermatitis and may also be valid for allergic vaginitis.[29]

Interestingly, in the majority of reported cases of allergic vulvovaginitis due to inhalants, the patients were children who have not developed *Candida* vaginitis because there was no estrogen in the vagina, essential for the overgrowth of the yeast.[6,30]

Foods and Drugs

Food or drug compounds may accumulate in the vagina and induce allergic reactions in susceptible women.[11–13] This may occur by ingestion or contact with the semen of a partner who had ingested the incriminating food or drug. In 1978, Haddad[15] reported the case of a woman allergic to walnuts who developed anaphylaxis on one occasion after sex with her husband. He had ingested walnuts prior to coitus and subsequent examination of his seminal fluid revealed the presence of walnut protein. In 1979, Simon et al[31] reported that recurrent candidiasis occurred after ingestion of banana in a woman with banana hypersensitivity.

In 1985, Green and Green[32] described a case of postcoital urticaria in a penicillin-sensitive woman who developed urticaria on three successive occasions following sexual intercourse. Direct questioning revealed that her partner was taking dicloxacillin for a skin infection. When a condom was used during intercourse, no symptoms developed and when antibiotic was discontinued, no adverse effects were observed after unprotected sex. Similar reactions have been reported with vinblastine,[33] mezlocillin,[34] and amoxicillin.[35]

Drugs may also affect the vagina and vulva for mechanisms other than type I hypersensitivity reaction. Examples are fixed drug eruption, contact dermatitis (to be discussed later), pemphigoid lesion.[36]

Semen

Allergic reaction to semen is a rarely diagnosed phenomenon, in spite of the increasing number of cases reported in recent literature.[37] In May 2000, 92 citations on semen allergy were found through MEDLINE searches since 1966. We may ask whether human seminal plasma allergy is a new and increasing phenomenon, or whether cases have previously occurred without being recognized. The exact incidence of hypersensitivity reactions to seminal fluid is unknown.[38,39]

It was first reported in 1958 by Specken, a Dutch gynecologist, a case of a 65-year-old woman who would have developed a generalized urticarial skin reaction after coitus, sometimes accompanied by asthma attacks, which would have disappeared after about 3 hours. Skin prick tests were positive to human seminal plasma but negative in controls.[38] In the English literature, such a reaction was first described in 1967 by Halpern et al,[2] when a 29-year-old atopic woman, after her first contact with semen, developed an anaphylactic reaction with giant urticaria, asthma, swelling of mucous membranes, and cardiovascular collapse. Skin and intradermal tests were positive to semen.

Subsequently, several investigators have described patients with a variety of clinical manifestations during and after intercourse. Bernstein et al proposed that patients with seminal plasma allergy can be classified into two groups, localized and systemic, depending on the character of the symptoms. These authors have also proposed a questionnaire survey in order to determine the prevalence of this disorder in symptomatic women.[39] They found that 12% of the women fulfilled the diagnostic criteria for human seminal plasma hypersensitivity.

In most cases, only vulvovaginal symptoms are elicited, which are often chronic and for which no cause is readily apparent. Mild local reactions may precede by months and even years the development of systemic reactions. Systemic manifestations range from generalized pruritus to severe hypotension and shock.[38,39]

In 1989, Presti et al[40] in a review article, observed that the majority of these women were 20 to 30 years of age and ⅔ of them were atopic. The condition occurred in monogamous as well as polygamous women, some of whom experienced symptoms at first intercourse. This phenomenon was also observed by Bernstein et al.[39] In this same study, a questionnaire survey demonstrated that there was a greater prevalence of self-reported food allergy among women with semen allergy.[39] These data suggest that these women may be reacting to seminal plasma proteins that cross-react with other common exogenous proteins (possibly foods) to which they may have been previously sensitized.[39] Many seminal plasma-allergic patients

were also reactive to the seminal plasma of different male partners.[43]

It has been clearly demonstrated that the systemic responses to human seminal plasma are immunologically mediated by the production of IgE antibodies. The disease is generally allergic and type I mediated, but type III and IV have also been reported. Clinical manifestations of postcoital arthritis, rash, hemorrhagic proctitis, bullous fixed drug eruption, and contact dermatitis after coitus have been described, with their respective diagnostic proofs.[38] Repeated episodes of asthma after unprotected sexual intercourse were due to semen.[41] The seminal plasma allergens have been characterized by gel-filtration chromatography and isoelectric focusing. Their molecular masses were reported to range from 12 to 75 kD and they are presumed to originate from the prostate gland.[42]

Although percutaneous skin testing tends to be specific for women with systemic reactions, it has not been a reliable marker for identifying women with localized reactions. The ultimate criterion for establishing a definitive diagnosis of either localized or systemic human seminal plasma hypersensitivity is the complete prevention of symptoms with the use of a condom. It is important to exclude seminal plasma transfer of food allergens or drug metabolites to susceptible allergic females.[39]

Male factors increasing the risk for semen allergy in women seem to be vasectomy, chronic illness, and infections. Female factors include pregnancy, infections, gynecologic surgery, and insertion of intrauterine devices. A high degree of HLA sharing between affected women and the partner has been suggested as a causal factor of the disease.[38,39]

Human seminal plasma allergy treatment includes the condom, systemic antihistamines, and intravaginal cromolyn sodium pretreatment in mild cases. Immunotherapy should be indicated with allergenic protein from the partner's seminal plasma. Patients with local hypersensitivity reactions are usually not considered candidates for immunotherapy. Successful cases of parenteral and intravaginal desensitization, with a successful pregnancy have been reported.[38,39,42,43] There is no consistent data on the unpredictable natural history of the disease.[38]

Latex

Natural rubber allergy is reported worldwide and it is responsible for a broad spectrum of allergic symptoms ranging from mild reactions to severe anaphylaxis.[3] It may determine type I or IV hypersensitivity reactions as a consequence of contact with latex used in condoms, diaphragms, surgical gloves, diagnostic[3] and surgical procedures.[44–46] With the increasing use of condoms to prevent sexually transmitted diseases, the incidence of latex allergy has also enhanced. Inhaled latex has also been reported to provoke vaginal pruritus.[16]

Semen + Latex

Unfortunately, some women present a concomitant allergy to semen and latex, becoming difficult to deal with these cases, if latex free condoms are not available. Non-rubber condoms, such as Lambskin, made from processed sheep intestines, can be used. It should be emphasized that such condoms do not protect against infection with human immunodeficiency virus. The male partner may wear a rubber condom and protect the partner's vaginal mucosa by placing a Lambskin condom over the rubber one.[38,47]

Candida albicans

In the 1900s, the incidence of vaginal candidiasis has increased dramatically. In the United States, the incidence has nearly doubled between 1980 and 1990. Although the condition is rare before menarche, by the age of 25 years, half of all college women will have had at least one physician-diagnosed episode of vulvovaginal candidiasis. It is not traditionally considered a sexually transmitted disease, since it occurs in celibate women and *Candida* is considered part of the normal flora. This does not mean that vulvovaginal candidiasis is not sexually associated. There is an increase in the frequency of such a disease when women begin regular sexual activity.[6,30]

The most interesting period in the history of the *Candida* infection began in the 1940s, when antibiotics were introduced for clinical use. Candidiasis, both mucocutaneous and systemic forms, has emerged as the most common opportunistic fungal disease, owing to the progressively increase in use of these drugs for both prophylactic and therapeutic uses.[30]

Recurrent vaginal candidiasis is defined as four or more episodes of infection per year, occurring in 5% of healthy women. It is a worldwide problem affecting millions of women and the pathogenesis is apparent in only some cases, including diabetes, antibiotic use, and immunosuppressive therapy.[6,30]

There is evidence incriminating *C. albicans* as a potent allergen. Both the protein and carbohydrate fractions of the yeast contain allergens. IgE against *C. albicans* associated with an immediate positive skin test, challenge test and clinical symptoms of allergy have already been demonstrated in the lungs, nose, and skin. Pulmonary allergy to *Candida* species is well documented.[48,49]

In 1988, Witkin et al identified *Candida albicans* specific IgE in vaginal washes.[9] In this study, a substantial number of women with recurrent vaginitis resistant to conventional treatment, were demonstrated to have IgE antibodies in their vaginal fluid, but not in their sera, reactive to *C. albicans*, pollen, spermicides, and seminal fluid. These data suggest that there are two kinds of allergic recurrent *Candida* vaginitis: (1) primarily due to *Candida* hypersensitivity and (2) secondary to other types of vaginal allergy, such as pollen, semen and latex.

Vaginal allergic response through the generation of PGE_2 would induce a transient and localized inhibition of cell-mediated immunity. An intact cellular immune system is essential to prevent overgrowth of *Candida.*

In 1994, Regulez et al identified *Candida albicans* IgE antibodies in vaginal washes of women with acute

Candida vaginitis-like, in whom the yeast was not identified in vaginal cultures.[50]

It is reasonable to assume that allergy is an important pathogenic factor in recurrent vaginal candidiasis.[51,52] Some authors report an important relief of symptoms with specific *C. albicans* immunotherapy in women, in whom all modalities of treatment had failed.[53,54]

Parasites

Parasites may cause several kinds of allergic reactions such as asthma and urticaria. Parasitosis due to *Enterobius vermicularis* (pinworm) is very common, especially in children. The migration from the anus to the vagina may cause an irritative and allergic vaginitis, that may induce eosinophilia and high total serum IgE antibodies.[55]

Spermicides

IgE anti-nonoxynol-9, the active component of spermicide jellies has been demonstrated in vaginal washes from women suffering from chronic vaginitis.[9] Furthermore, studies have demonstrated that nonoxynol-9 was toxic to lymphocytes and macrophages and significantly inhibited their function.[19]

Contact and/or Irritant Dermatitis of the Vulva

Allergic contact dermatitis is an important, but often unrecognized factor in vulvar pruritus and can be caused by a great number of substances in our environment. A detailed medical history is necessary to clarify the offending substance. Irritant contact dermatitis occurs as a result of friction and trauma, or due to the use of corrosive chemicals.[56]

It should be emphasized that these compounds may be in use by the patient or her partner as topical medication on his genitalia, shaving cream, after shave lotion, nail polish, etc. Several agents may cause vulvar symptoms.

Topical medications. In a recent study among 121 patients with vulvar contact dermatitis, medications, or their constituents were the most common allergens.[57] Over-the-counter antibiotic, anti-fungal preparations, and anesthetics (used by males to delay ejaculation) are well-recognized skin sensitizers.[56,57] Women suffering from allergic reactions to vaginal moistures is a common situation.[57]

K-Y jelly. This is a useful aid for those women who fail to lubricate adequately during sex. Symptoms are due to propylene glycol in the preparation. This substance is also widely used as a vehicle for cosmetics, body lotions, antiperspirants and topical medicines.[58]

Perfumes, hygiene sprays, soaps, "bubble-bath", etc. Contact dermatitis to perfume and one emollient has been reported by Fisher.[59] It may be used by women or the male partner in shower gel, lotions, perfumes, etc.

Nail polish. A widely used cosmetic and a very common sensitizer. Allergies to nail polish, its remover and artificial nails should be included in the differential diagnosis of vulvar contact dermatitis.[56]

Sanitary napkins. A great variety of different sanitary napkins has been introduced into the markets of industrialized countries in recent years. Some women do not restrict their use to the menstrual period, but use them daily, in order to be "comfortable and hygienic." Fragrances, plastics, glue, and disinfecting agents are commonly incorporated into the pad and may produce contact urticaria and dermatitis. A recent Canadian study revealed "Always" sanitary napkins (frequent minipad use) as a potentially important cause of recurrent vulvitis. Physician awareness of this association will afford effective advice and relief for a large number of women suffering from "chronic vulvovaginitis."[60]

Soaps and detergents used in underwear washing. The use of soaps, synthetic detergent and other laundry products has been associated with skin dryness and aggravation of dermatologic conditions.[61] Residues of these products on the underwear may cause vulvar irritation.[62] This is partly due to their alkaline nature and presence of formaldehyde and enzymes.[61] *Bacillus licheniformis* protease present in the commercial identical enzymes (Alcalase and Maxatase) are used in household detergents. These enzymes may cause irritation, microscopic erosion of vaginal mucosa and IgE-mediated reaction.[63]

Saliva. A rare condition associated with oral sex. The labia minor and clitoris are particularly affected. Persistent vulvar inflammation, with no infection in the vagina and no probable contact with allergens may be due to orogenital contact, which is a common practice among all classes of mammals. Saliva is a complex fluid containing a variety of minerals, proteins, amilase and bacteria. It is not possible to establish whether it is the saliva alone or a bacterial infection transmitted by the salivary deposition which has caused the inflammation. In the latter situation the partner must also be treated.[64]

Newsprint. It has been reported that bedtime newspaper readers produced a genital hypersensitivity reaction in their female sexual partners by transferring newsprint during sexual foreplay.[65] Coal tar, colophony, aluminum, acrylamide, and diazopaper are the most important sensitizer agents. Symptoms may also affect the eyes and the respiratory tract.[66]

Colophony. There is in the literature an interesting case of a violoncellist who had suffered from vulvar pruritus for 15 years.[67] Patch tests revealed a positive reaction to colophony. Rosin used to wax the strings of musical instruments contains colophony. It is interesting to note that she did not develop dermatitis by handling the rosin, but in a distant organ, the vulva. It has been suggested that some substances (such as nail polish causing eczema on the eyelids) can cause more intense reactions on the vulva than other sites.[12,68]

Textile dermatitis. The true incidence of irritant and/or contact dermatitis to clothing is unknown. Textile dermatitis remains largely underreported, because many cases do not conform to the classic clinical pattern and are therefore not diagnosed. Textiles are made from natural or synthetic

fibers, either alone or in combination. These fibers are usually woven, but may be matted, such as felt. Natural fibers are cellulosis (cotton and linen) or proteinaceous (silk or wool). Man-made fibers are derived from cellulose polymers (rayon and acetate) or are manufactured from synthetic polymeres (nylon, polyester, acrylic, spandex, etc).[69]

Fibers are rare causes of contact dermatitis. By contrast, chemicals used on textiles are a frequent cause of such a condition. Since the 1930s, formaldehyde compounds have been used on textiles to make them crease-resistant or shrink-proof. Textiles not treated with finishing substances are 100% cotton denim, 100% linen, 100% wool, and 100% silk. Textiles likely with finishing substances include rayon, lycra, any blend of cotton, rayon or wool, blends of synthetic and natural fibers.[69]

Textile dyes are other common cause of contact dermatitis. It is believed that dyes are a more frequent cause of dermatitis than formaldehyde resins. The incidence of dye allergy has been estimated as 1.4% to 5.8% of all patients with eczema, and it appears that women are affected more often than men by dyes in their clothing. Disperse Blue 124 used on black, synthetic, stretchy for leggings, jeans, bodies, aerobic outfits and underwear is one of the most common sensitizer dyes. Other are Disperse Yellow 3 and Disperse Red 1. It is suggested that sweat plays a major role in the transfer of dye from clothes to skin and its absorption into the skin.[69]

Use of pants, jeans, and underwear which contain textile sensitizers, textile finishing, or dyes may be an important cause of unrecognized vulvovaginitis.[68,69]

Miscellaneous

Atopic dermatitis can also affect the vulva. It is characterized by severe pruritus, xerosis of the skin, and particularly lichenification.[70]

Urticaria may sometimes affect the female genital tract. Erythematous pruritic skin lesions tend to be evanescent in the labia maiora, labia minora, and clitoris. Angioedema may also be present and can occur in the vagina.[38,40,45,70]

Dermographism may occur in the vulva and worsened by the use of tight underwear.[71] Dermographism that occurs only after sexual intercourse is not a rare condition and it may be associated with exercise-induced (by the sexual intercourse) urticaria.[65,70]

Drug eruption in the genitalia is sometimes seen in the allergist's office. The characteristic lesion is well delineated, round or oval, mildly pruritic or may produce a burning sensation. It is considered to be virtually pathognomonic of drug hypersensitivity. Drugs most commonly implicated include phenolphthalein, analgesics/antipyretics, barbiturates, penicillins, sulfonamides, tetracycline, and minocycline.[38,70–72]

There are patients who come to the allergist's office complaining of "allergy" from their husband's sweat, and a very interesting case was reported by Freeman in 1986.[73] A 46-year-old woman presented a history of severe urticaria after having sexual intercourse or any other type of physical contact with her husband. She had a positive immediate skin test to both, his semen and sweat. She also showed a positive skin test to her two son's sweat. She solved her problem, at least temporarily, by leaving her husband.[73]

There are four *risk factors associated with allergic vulvovaginitis.* (1) *Sexual intercourse.* A detailed history taken from women with recurrent vaginitis are closely related to sexual activity, which may act in the following ways:

- microscopic abrasions of vaginal mucosa involving the act, possibly in association with inadequate lubrication,[53]
- immunosuppressive activity of semen, which can be accounted for the very high levels of PGE_2 and extracellular organelles (protasomes),[74]
- IgE-mediated disease caused by semen,[37–43]
- change in pH,[53] and
- psychologic symptoms caused by frustration and unhappiness after an unpleasant sexual intercourse.[75,76]

(2) *Exaggerated personal hygiene habits.* Generally in adult women, studies have shown that chemicals used in excess for either cleansing of external genitalia or vaginal douching were a significant risk factor for recurrent candidiasis.[77]

(3) *Dressing patterns.* In a 1982 study, an increased recovery rate of *Candida albicans* was observed in wearers of tight clothing in association with nylon or lycra underwear propitiating more warmth and moisture conditions in the female genitalia.[78] Jeans and pants should also be avoided by susceptible women.

(4) *Psychologic factors.* In 1998, Irving et al demonstrated that women with recurrent vaginitis were significantly more likely to suffer clinical depression, to be less satisfied with life, to have poorer self esteem, and to perceive their lives as more stressful.[79] Sexual insatisfaction and anorgasmia is very common in this group.[76] There is no doubt of the frequent association between tension and pruritus, but the question is, Are these findings a cause or a consequence of the chronic vaginal pruritus, dyspareunia, and discharge caused by the release of chemical mediators of the allergy in the genital tract? Treatment should also be directed at the sexual dysfunction and marital discord that frequently accompany chronic vaginitis.[6,76,79]

DIFFERENTIAL DIAGNOSIS

Vaginitis is one of the most common problems in clinical medicine and a careful differential diagnosis should always be done by the gynecologist before sending a patient for an allergic evaluation (Table 1). *Trichomonas*, *Gardnerella*, *Mycoplasma*, *Chlamydia trachomatis*, herpes simplex virus, human papillomavirus (HPV), aerobic and anaerobic bacteria, AIDS, and other sexually transmitted diseases are common etiologic agents of vaginitis.[6,30,70]

Other diseases of the skin as psoriasis, lichen, pemphigus, lupus, pelagra, Behcet's syndrome, and Paget's disease can itch and burn. Vulvodynia occurs with irritant and allergic derma-

Table 1. Differential Diagnosis of Vulvovaginitis

	Allergic	Non-allergic
Type I—IgE mediated	Inhalants (house dust mites, pollen, latex), foods, drugs, semen, latex, *Candida albicans*, parasites, spermicides, enzymes	———
Type IV—contact dermatitis and/or irritant	Topical medications, K-Y jelly, perfumes, hygiene sprays, "bubble bath," shower gel, after shave lotion, nail polish, sanitary napkins, soaps and detergents, saliva, newsprint, colophony, textile	———
Miscellaneous	Atopic dermatitis, urticaria, dermographism, drug eruption	———
Infectious	———	*Gardnerella vaginalis*, *Mycoplasma* sp, anaerobic lactobacilli, *Chlamydia*, Herpes simplex virus, HPV, HIV, *Candida albicans*
Diseases of the skin	———	Psoriasis, lichen, pemphigus, lupus, pelagra, Behcet's syndrome, Paget's disease
Other	———	Sexual abuse, foreign body, poor hygiene, psychologic, idiopathic

titis, but also as an idiopathic (dysesthetic) form.[70,80]

In children, poor hygiene, foreign body, and sexual abuse should be investigated and excluded.[6,30,81]

PRACTICAL APPROACH TO THE PATIENT

Patient History

The most important characteristic of a patient who consults an allergist is that she has already been evaluated by at least two gynecologists, who have already excluded systemic diseases, use of antibiotics, corticosteroids, or immunosuppressive drugs. Several of these women are ordered to stop oral contraceptives.[52–54,63,64,67]

Potential causes of vaginal infections (*Trichomonas*, *Gardnerella*, *Mycoplasma*, aerobic and anaerobic bacteria, AIDS, and HPV) have also been excluded. *Candida albicans* is the only pathogen incriminated in the majority of cases in adult women and they and their partners have been exhaustively treated with local and systemic antifungal agents.[9,28]

In children, after excluding poor hygiene, presence of intravaginal foreign bodies and sexual abuse,[80,81] usually no pathogen is identified. Even so they are frequently treated with antibiotics.[28] Parents may notice the child crying during urination[25,26] and scratching herself repeatedly. Often the child's pediatrician will have evaluated the child for urinary tract infection. Evaluation of pinworms is also warranted.

In an adult woman, symptoms usually consist of pruritus, vulvar burning, dyspareunia and unodourous vaginal discharge, which may be clear or resembling cottage cheese, when there is *Candida* infection. In the majority of the cases of hypersensitivity to inhalants, semen, and *Candida albicans* there is a familial history of allergy as well as symptoms of the disease in other organs, such as rhinitis, asthma and conjunctivitis.[9,24–28,38,52–54] Semen allergy is associated with food allergy.[39]

Several patients complain that "everything" irritates her vagina. In the majority of cases, sexual intercourse worsens the condition, regardless of the etiology of the allergy. During the act, they have difficulty to support the friction of the penis inside the vagina.[17] Heat, warmth, swimming, the use of tight jeans, lycra underwear, and psychologic disturbances are also triggering factors.[6,17,30] Vacations at the beach usually cause marked worsening of the vaginitis.[17] All these evidences lead us to consider a clinical form of vaginal hyperreactivity. In 1988, Sonnex[65] described "sexual hypersensitivity." The difference is that we observe other nonspecific factors besides intercourse.[17]

Information should be collected about the type of used sanitary napkins, frequent use of minipad (nowadays common among women), and the type of soaps used to wash the underwear. Dressing patterns, clothing preference, and soaps used to wash the panties should be investigated.[60,61–63,68,69,78]

Physical Findings

Vulvar erythema, excoriation, lichenification, and fissuring are the most common clinical findings. This is often localized to the mucocutaneous margins of the vaginal introitus and the fourchette, but it can spread to affect the labia majora and the perineum. Sometimes, the labia minora and clitoris are also affected. Discharge can be or not present.[6,23–28,30,64,70,80,81]

Laboratory Evaluation

After gynecologists have excluded systemic diseases and/or treated any pathogen, some laboratory evaluations are the responsibility of the allergists. These include the following:

1. prick and/or intradermal skin test using common inhalants (house dust mites, pollen, animal epithelium, etc) foods, suspected drugs, *Candida albicans*, latex, semen, spermicides, and enzymes,[9,23–29,32–35,39,45,48–54,63]
2. total and specific serum IgE to these allergens,[9,28,50]
3. specific IgE antibodies in vaginal secretion,[9,20]
4. total eosinophil counts in vaginal secretion,[10,28] and
5. Patch tests with suspected substances in cases of contact dermatitis. Common vulvar sensitizers are propylene glycol, antibiotics, antifungals, parabens, formaldehyde, colophony, coaltar, dyes, etc.[66–69]
6. Vaginal provocation test with the suspected allergens. This would be the ideal procedure to reproduce a vaginal allergic response. IgE and eosinophils could be monitorized.[9]

Nevertheless, patients often do not give informed consent for such a procedure.

Treatment

Patient education. Women suffering from any type of allergic vulvovaginitis should be educated to change their behavior in order to alleviate vulvar irritation. These include removal of the offending agent (when and if it is recognized), avoidance of all topical medications as well as deodorant sprays, perfumes, alkaline and colored soaps, bubble bath, chemical douches, depilatory and shaving creams. Too frequent cleansing habits should be avoided, as these reduce the natural protection of the vagina and alter the flora.[17,59–63,77]

Women should use unscented tampons and sanitary napkins, preferentially more simple products, with no "protective wings," because these adhesive wings contain more glue, which melts with perspiration and can cause pruritus and sensitization.[17,60] Doctors should explain to the patient that the vagina is a "damp" organ, that physiologic secretions are normal and that frequent use of minipad may avoid the local ventilation, facilitating the development of yeast and causing sensitization.[17,60] She may also use white and unscented toilet paper.[17,69]

Dresses and skirts should be preferred to long pants. Jeans material is too thick for the female genital area and tight-fitting clothes should be avoided. Elastic swimming and gymnastic clothes should be removed as soon as possible. Underwear should be white and 100% cotton and the patient should be encouraged to sleep without her underwear, so that the area can "breathe" for a few hours.[17,69,78]

A non-perfumed, non-enzyme soap should be chosen for clothes washing. Rinse thoroughly to remove detergent residue. Underwear should not be washed in the shower or dried in the bathroom. They should also be ironed. Before using newly purchased panties, they should be carefully washed. In case of pollen allergy, the clothes should be dried indoors, never outside.[17,27,61–63,69]

During sexual intercourse, penetration should be avoided in the absence of an adequate lubrication, because an intact vaginal mucosa prevents invasion of normally colonizing organisms. The patient should avoid the permanence of semen inside her vagina (unless she wishes to become pregnant) by sitting on the toilet and with a pushing movement to expel the semen (Valsalva Maneuver).[17] This is due to immunosuppressive effect of the sperm, which alters the vaginal pH. Internal douches and external cleansing with soaps after the intercourse should not be used, because chemical agents may exacerbate irritation of the mucosa due to the natural friction during coitus.[17,61,62,74]

Women should also be advised to perform an environmental control of inhalants, if she is sensitized to them and specially check if there is mold in the drawers and closets where underwear is stored.[17,27,28]

Antihistamines. Prophylactic antihistamine therapy has variable results. Few case reports show that oral antihistamines appear to be effective in the management of the pruritus in allergic vulvovaginitis,[22,27,28] including cases of semen allergy.[38] There is not an open or double-blind study with antihistamines in allergic vulvaginitis.

Cromolyn sodium. Local administration of cromolyn sodium, a mast cells stabilizer, also improves symptoms in some women with allergic vaginitis.[28,82,83] In mild cases of semen allergy, it has been used before sexual intercourse.[38] Similar to antihistamines, there is not an open or a double-blind study demonstrating its effectiveness.

Corticosteroids. There is a case report on allergic vaginitis due to ragweed, in which no success was obtained with antihistamines for controlling the symptoms. Prednisone was provided for the ragweed season and complete control was achieved.[27]

Immunotherapy. (1) Inhalants. A series of case reports shows important improvement of symptoms after immunotherapy for allergic vulvovaginitis due to pollens[24–27] or house dust mites.[28]

(2) *Candida albicans.* There are in the literature five case reports[52] and five open studies,[53,54,84–86] including 177 patients suffering from recurrent vaginal candidiasis who had been prescribed *Candida albicans* allergen immunotherapy. These women had positive immediate skin test to yeast and showed improvement ranging from 65% to 80%.

All of these women had been referred to allergists because all other treatment modalities had failed. There is not a double-blind placebo control on *Candida albicans* allergen immunotherapy, but it seems to be the only alternative therapeutic modality for these women.

(3) Human seminal plasma. There have been several reports attempting to treat human seminal plasma anaphylaxis by subcutaneous immunotherapy with whole seminal fluid[87] or a fraction of seminal fluid[42] with various protocols and variable success. Bernstein et al[39] affirm that they had 100% success with such a treatment. In this review of the literature, we could not precisely confirm the number of these women.

The intravaginal route is another described alternative. Until 1999, there were three cases of successful intravaginal desensitization with human seminal plasma, but a mean period of 3-days interval between each intercourse is necessary to maintain the desensitization state.[43]

Immunotherapy is a procedure that should always be conducted under the supervision of an allergist, a physician who is adequately trained and familiarized with the subject.

SUMMARY

It is important to recognize the existence of allergic vulvovaginitis caused by different agents, so that time is not lost in searching and erroneously treating for other causes rather than allergy in the management of the intense and prolonged symptoms of the genitalia.

In this review we have described the pathophysiology, the diverse forms of allergic vulvovaginitis, and its differential diagnosis. Differential diagnosis in relation to other nonallergic vulvovaginitis was also included. We emphasized the practical approach to the patient, describing the patient's history, physical findings, laboratory evaluation, and treatment. Special attention was given to patient education in order to change behaviors that might alleviate their symptoms with nonpharmacologic measures.

Surprisingly, some data presented in this review were initially unknown to us, the authors, and maybe also to you, the readers. Entering the new millennium, there will for instance be some physicians astonished at the possibility of house dust mite or food allergens sensitizing the vagina. We may ask whether many vaginal diseases treated as "infection" are not some types of misdiagnosed allergy or even a secondary infection after a primarily allergic phenomenon. In a major textbook of medicine edited in 2000[88] we read, "Infections of the female genital tract produce a variety of syndromes, often with overlapping symptoms. These are very common, relatively poorly understood, sometimes difficult to treat and often frustrating for both doctor and patient."

Interestingly, in a textbook of medicine written in 1878,[89] we found the following citation relative to leuchorrea: ". . . It is extremely common in big cities and can be said without exaggeration, that this illness affects indistinctly married ladies and widows, and may even, at times, affect girls of 4 to 8 years of age. The predisposing factors are habitation in humid and badly ventilated places, abuse of lacteous and farinaceous foods, and the sadness of the spirit. It is exceedingly difficult to cure this affection. There are women who suffer from this malady their whole lives. In order to cure this illness, it is necessary to move little girls to spacious and well ventilated houses . . ."

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CME Examination
Identification No 2000–010
Questions 1–20. Moraes PSA and EA Taketomi. Ann Allergy 2000;85;253–267.

CME Test Questions

1. Vaginal protective mechanisms against pathogens include, *except*:
   a. Mucosal secretory immunity
   b. Bioactive reproductive secretions
   c. Metabolites from commensal organisms
   d. High pH
   e. Cyclic menses
2. Which is the main protective factor against yeast infection in the vaginal mucosa?
   a. Humoral immunity
   b. Cellular immunity
   c. Complement system
   d. Phagocytosis
   e. Antibody dependent cellular cytotoxicity (ADCC)
3. All the following statements are true, *except*:
   a. In healthy women, penicillin reaches maximum level in the serum and saliva 1.5 hours after oral ingestion, and its concentration in the vagina continually increases over a 15-hour period.
   b. Ingested compounds may accumulate in the vagina.
   c. Vaginal penicillin, steroids hormones, seminal fluid, and prostaglandins cannot be systemically absorbed.
   d. Studies indicate that there is a countercurrent blood flow in the female genital tract.
   e. The human vaginal basal lamina contains macrophages, lymphocytes, plasma cells, Langerhan's cells, eosinophils and mast cells.
4. Class II major histocompatibility antigens (HLA-DR) in vaginal mucosa are especially present on the surface of:
   a. Langerhan's cells
   b. T lymphocytes
   c. Eosinophils
   d. Macrophages
   e. Mast cells
5. Which mediator of allergic reaction suppresses vaginal cell-mediated immune response?
   a. Histamine
   b. Leukotriene E_4
   c. Platelet activating factor (PAF)
   d. Bradicinine
   e. Prostaglandin E_2
6. All of the following statements are true, *except*:
   a. Hormone secretion is influenced by immunologic factors and vice-versa.

b. Progesterone induced-mitosis in the vaginal mucosa results in epithelial thickening.
c. There is an immunosuppression in the vaginal mucosa during menses and periovulatory phase.
d. Under the influence of progesterone interepithelial vaginal channels become diluted during the luteal phase of the cycle.
e. Progesterone favors the development of Th2 helper cells.

7. Which of the following inhalants has been reported to provoke allergic vulvovaginitis?
a. House dust mites
b. Latex
c. Pollen
d. All of the above
e. None of the above

8. Inhalant allergens may reach vaginal mucosa through of the following routes, *except*:
a. Direct contact
b. Systemic absorption
c. Clothes
d. Semen
e. Fingers

9. Inhalant-induced vaginitis is more commonly diagnosed in:
a. Sexually active women
b. Pre-puberal girls
c. Puberal girls
d. Post-menopausal women
e. Celibate women

10. How does a vaginal allergic reaction predispose a woman to a *Candida* infection?
a. By release of histamine, which is a potent inducer of prostaglandin E_2.
b. By generation of leukotriene, which is an inducer of transforming growth factor β.
c. By production of eosinophil chemotactic factor, which is an inducer of interleukin-10.
d. All of the above.
e. None of the above.

11. All the following statements concerning vaginal allergic reactions are true, *except*:
a. Vaginal allergy may be caused by foods and drugs.
b. It may occur by ingestion or contact with the semen of the partner who had ingested the food or drug.
c. Orally ingested compounds cannot accumulate in the vagina.
d. Foods may worsen some cases of recurrent vaginal candidiasis.
e. Some drugs may cause a bullous fixed eruption in the vulva.

12. Human seminal plasma hypersensitivity is more common in women of which group?
a. 20–30 years of age
b. 30–40 years of age
c. 40–50 years of age
d. During the pregnancy
e. After the menopause

13. Which of the following allergies are associated with semen allergy?
a. Asthma
b. Contact dermatitis to nickel
c. Food allergy
d. Latex allergy
e. Ocular allergy

14. The molecular weight of the seminal plasma allergens have been reported to range from:
a. 2 to 12 kDa
b. 12 to 75 kDa
c. 75 to 100 kDa
d. >100 kDa
e. None of the above

15. The ultimate criterion for establishing a definitive diagnosis of either localized or systemic human seminal plasma allergy is:
a. Positive skin test
b. High levels of specific IgE
c. Complete prevention of symptoms with the use of a condom
d. Positive vaginal provocation test
e. Positive skin test and vaginal provocation test

16. All the following statements are true, *except*:
a. Patients with human seminal plasma allergy should be classified into two groups, localized and systemic, depending on the character of the symptoms.
b. It is not possible to develop semen allergy at the first intercourse, since a sensitization period is necessary in these cases.
c. Human seminal plasma usually induces allergic reaction type I, but type III and IV have also been reported.
d. Percutaneous skin testing tends to be more specific for women with systemic reaction.
e. In women risk factors for semen allergy are pregnancy, infections, gynecological surgery, and insertion of an intrauterine device.

17. Lambskin condoms, made from processed sheep intestines are not effective to:
a. Prevent an allergic reaction to semen
b. Prevent against a pregnancy
c. Protect against HIV infection
d. Protect against syphilis infection
e. Protect against gonorrhea infection

18. Recurrent vaginal candidiasis (four or more episodes of infection per year) occurs in:
a. 5 percent of healthy women
b. 15 percent of healthy women
c. 30 percent of healthy women
d. 50 percent of diabetic women
e. 50 percent of women under corticotherapy.

19. All the following statements are true, *except*;
a. *Candida* vulvovaginitis is not traditionally considered a sexually transmitted disease, but there is an increase in the frequency when women begin regular sexual activity.
b. *Candida* vulvovaginitis is very common before menarche and after the menopause, because vaginal mucosa in these groups is thin and atrophic.
c. Much evidence incriminates *C. albicans* as a potent allergen. Both the protein and carbohydrate fractions of the yeast contain allergens.
d. Recurrent vaginal candidiasis

can be primarily due to *Candida* hypersensitivity or secondary to other types of vaginal allergy, when there is a generation of PGE_2.

e. Immunotherapy with *C. albicans* may be useful in some women in whom all modalities of treatment have failed.

20. Women suffering from allergic vulvovaginitis should be instructed to:
    a. Perform environmental control if she is allergic to mites, molds or animal danders, washing underwear with soaps containing enzymes, avoid special deodorant sprays and hygiene products.
    b. Avoid all topical medications, wear white 100% cotton underwear, sleep in their underwear.
    c. Wear white 100% cotton underwear, avoid jeans and pants and cleanse external genitalia 6 times a day.
    d. Wear white 100% cotton underwear, use unscented sanitary napkins and toilet paper, and perform environmental control if she is allergic to mites, molds or animal danders.
    e. Use extra rinses for washing clothes, use a frequent minipad to be comfortable, avoid topical medications.

"*He who knows all, says nothing. He who says all, knows nothing.*" —*Lao Tse*

Answers to CME examination—Annals of Allergy, Asthma & Immunology (Identification No 2000-009) Tamada K and L Chen. T lymphocyte costimulatory molecules in host defense and immunologic diseases. Ann Allergy Asthma Immunol 2000; 85:164–176.

1. c	2. e	3. d	4. c
5. a	6. b	7. d	8. e
9. b	10. d	11. d	12. d
13. b	14. e	15. c	16. a
17. b	18. e	19. e	20. e