

# Colposcopy of the vulva, perineum and anal canal

CHAPTER

14

# Colposcopy of the vulva, perineum and anal canal

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## INTRODUCTION

Colposcopy of the vulva – vulvoscopy – is an important part of gynaecological examination. However, it does not provide as much information about the nature of vulvar lesions as colposcopy of the cervix. This is due to the normal histology of this area, which is covered by a keratinized, stratified squamous epithelium. The multifocal nature of vulvar intraepithelial disease makes the examination more difficult. Nevertheless, colposcopy should be performed in the examination of vulvar pathology because of its importance in identifying the individual components of the lesions, both for biopsy and treatment purposes. Anatomically, the vulva, the term that designates external female genital organs, consists of the mons pubis, the labia majora, the labia minora, the clitoris including frenulum and prepuce, the vestibule (the vestibule, the introitus), glandular structures that open into the vestibule and the hymen. Colposcopically, the vulva includes the external urethral orifice, the perineum, the perianal area and the anus (*Figure 1*).

The embryological origin of these structures differs. The epidermis of the vulvar skin and its appendages are of ectodermal origin. The dermis is derived from the mesoderm. Vestibule is the only structure that originates from the endoderm, like the bladder and urethra. Consequently, the histology of these structures is not the same. Vulvar skin which has ectodermal origin consists of epidermis which is keratinized, non-glycogenated stratified squamous epithelium and two layers of dermis (papillary and reticular), that are situated over the underlying fat tissue.

Mons pubis, lateral parts of the labia majora and the perianal area are covered by hair-bearing skin. The hair, the hair follicle, the sebaceous gland, the errectores pillorum muscle and the apocrine glands form a distinct functional unit – pilosebaceous unit. Eccrine sweat glands are also present. The inner parts of labia majora, entire labia minora and clitoris are covered by non-hair-bearing skin. These areas are richly provided with sebaceous glands which open directly onto the skin. The vestibule is covered by non-keratinized squamous epithelium. It contains mucus secreting glands.

In the attempt to colposcopically examine the vulva, it is essential to know the histology of vulvar skin since the appearance of the lesion largely depends on the tissue structure of the affected site. Besides its own special properties of the structure, vulvar skin has specific functional features. The physiology of the vulva follows the principles of all other parts

of the female reproductive system. The vulva is responsive for the sex steroids. The alterations that are clinically recognizable in the vulva throughout life and additional cyclic changes, occurring during the reproductive period, are the result of sequential variations of ovarian hormone secretion. Significant changes happen during puberty, sexual intercourse, pregnancy, delivery, menopause and the postmenopausal period, which alter the external appearance and function of the vulva. Knowledge about this cyclical activity is important in diagnosis and treatment of vulvar disorders.

It should be remembered that the vestibule, as an endodermal derivate, is less sensitive to sex hormones than adjacent structures. This should be taken into consideration during the treatment of certain vulvar conditions such as vestibulitis.

## TISSUE BASIS OF COLPOSCOPY OF THE VULVA

The colposcopic image of different vulvar lesions depends on the features of the tissue examined. The most important ones are the thickness of the epithelium and the vascularity of the underlying stroma. Thickness of the skin affects the opacity. It varies from one person to another and in between different areas of the vulva. Skin of hair-bearing parts is thicker than the skin of other areas of the vulva. This is why histologically identical lesions may have different appearance when present on different parts of the vulva. Vulvar epithelium is predominantly dry. Its prominent surface keratin layer does not provide a clear view of the underlying blood vessels. Pigmentation can also obscure blood vessels. Therefore vascular patterns are less marked and less reliable than with colposcopy of the cervix. Vascular aberrations such as punctations and mosaic patterns do not easily develop on vulvar skin. They are less common and can be practically seen only on the non-hair-bearing areas. These are the inner portions of the labia minora where the keratin layer is thinner and vestibular epithelium that does not contain a keratin layer.

Thus, leukoplakia and acetowhite epithelium are the most frequent colposcopic manifestations of vulvar pathology. Stromal changes that influence colposcopic appearance are usually due to the increase in vascularity. This increase may be part of an inflammation, an immune response or the neovascularisation of neoplasia. In these cases, the colour of the skin will become red. The vascularisation may also be decreased or stroma may undergo fibrotic changes, which result in whitish colouring of the skin.

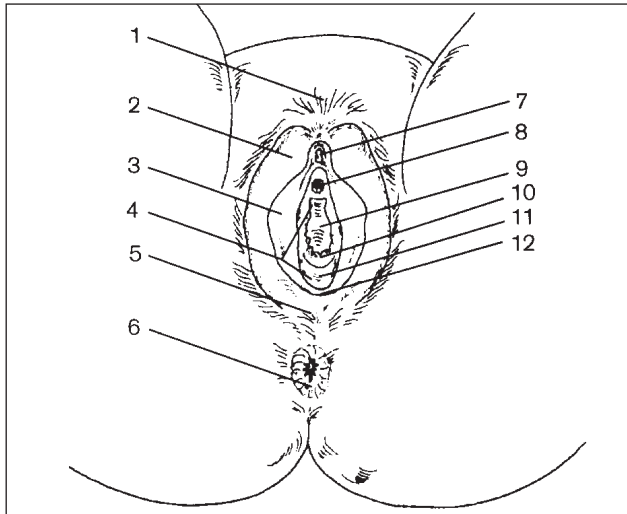


Figure 1. Drawing of the vulva: anatomical elements

## TECHNIQUE OF COLPOSCOPY AND BIOPSY OF THE VULVA

The technique of colposcopy of the vulva does not differ from usual colposcopy examinations of the cervix. The patient is examined in a lithotomic position. This examination can be unpleasant and even painful for some women. Therefore it is necessary to perform it gently, but thoroughly. All parts of the vulva have to be examined: labia majora and minora, vestibule, clitoris, terminal urethra, perineum, perianal regia, and anus up to its muco-cutaneous junction. It may also be wise to carry out a colposcope examination of the anal canal if the patient is tolerant to such an examination. This is performed with the aid of a proctoscope. The examination has several stages.

### VISUAL EXAMINATION – INSPECTION

The examination of the vulva should start by visual examination of the entire vulvar region. Simple examination usually offers adequate visibility of mons pubis, labia major, the rim of labia minor, perineum and anus. Attempt should be made to clearly visualize the hair-bearing skin. Proper examination requires separation of labia majora and minora and the exposition of entire vesitibule in view (Figure 2a-b).

This part of the examination is particularly important because it reveals fields of redness, hyperkeratinization (leukoplakia), pigmentations, ulcerations and atrophy. Genital warts or invasive cancer can be easily recognized. Application of water-soluble lubricant, analogue to examination with saline in colposcopy of the cervix, decreases the keratinizing effect to a certain extent and assists in the visualization of abnormal vessels.

### APPLICATION OF ACETIC ACID

Application of acetic acid is the next, very important stage of vulvoscopy. Many otherwise undetected lesions, particularly



Figure 2. a) Vulva before proper examination, i. e. exposition of inner part of the labia minora and vestibule. b) The same patient after proper exposition of the vulva (atypical changes visible in between labia minora).

HPV lesions may present as white areas. The lesions will appear as shiny acetowhite patches with a spiculated or micropapillary surface. Punctuation and mosaic do occur on the mucosal surface of the labia minora, and should be searched for. Compared to the examination of the cervix, the acetic acid has a less prominent effect on the vulva. To make the examination of the keratinized skin more efficient, acetic acid should be applied frequently, in large amounts and in a more concentrated solution (5%). The application has to be long enough, usually 2-3 minutes, to allow vulvar lesions to show. A useful way to achieve this is to compress a gauze swab soaked with acetic acid against the vulva.

Colposcopy should begin using the lowest magnification (6x) to quickly scan the vulva. Later, it can be proceeded to higher magnifications, as necessary, to examine smaller satellite lesions. Keratosis aggravates the normal opacity of the vulvar surface. In such cases, the magnification afforded under good lighting aids delineation of the lesions.

### COLLINS TEST

The test that uses a solution of toluidin blue to mark vulvar lesions is known as the Collins test (1). Toluidin blue is a nuclear stain that fixes to surface cell nuclei when applied in vivo. All foci of nuclear activity will keep the colour and become stained (Figure 3). This may happen not only in neoplasia but also in the presence of ulcerations, lacerations, reparative changes and parakeratosis. Therefore, although useful, this test was not considered specific enough. However, it has recently been reported that the toluidine blue test is an inexpensive and reliable method of separating vulvar intra-epithelial neoplasia (VIN) from hyperplastic, non-neoplas-



Figure 3. Collins test

tic epithelial disorders, and choosing a biopsy site on the vulva (2).

Collins test is performed by applying 1% aqueous solution of toluidin blue to the skin carefully cleaned of ointment or powder. The application should take 2 minutes. Afterwards, vulvar epithelium is discoloured by rinsing with 1% acetic acid. The stain will be entirely washed from normal skin

because surface epithelium does not contain nuclei. Any condition that results in the presence of nucleated cells on the skin surface will retain the colour which will be visible as fine blue spots that can be identified under colposcopic examination.

## BIOPSY

Vulvoscopy can localize the lesion exactly. It usually cannot predict the histological nature of the lesion. Proliferated tissue with an abnormal vascular pattern is always suspicious of invasion. However, the majority of vulvar lesions does not have specific characteristics. Therefore, the diagnosis of a vulvar lesion always requires biopsy. Biopsy is mandatory in: 1. fast growing lesions, 2. ulcerations, 3. areas of bleeding, and 4. each suspicious area of any colour.

Large lesions and multicentric lesions will require multiple biopsies. Vulvar biopsy is relatively easy to perform using a variety of instruments. The procedure may be painful and it is always useful to minimize the discomfort of the patient by applying local anesthesia. The biopsy site can be anaesthe-

tised by injecting 1% xylocain (lidocain) or 3% prilocain solution by a fine needle, subepithelially or subdermally. Apart from anesthetic effect, the injection lifts the skin and the biopsy will be easier. An attempt should be made to get a specimen, at least 5 mm thick.

Keyes instrument (Keyes punch forceps) is often used for punch biopsy of the vulva. It will remove a round skin area of desired diameter. Usually, 3-5 mm punch forceps are chosen. The procedure is performed by firmly pushing the punch into the skin with a rotation action. The depth will depend on the sharpness of the instrument and the pressure applied, as well as of the thickness of the epidermis. When the instrument reaches the dermis, the resistance is decreased. If at this point further pressure is applied, there is the risk of going too deeply, which can cause severe bleeding. Fine tissue forceps or scissors are necessary to detach the specimen from the dermal tissue. The defect that remains after the biopsy can be left open to heal spontaneously. Healing takes 2 weeks. Monsel's solution (ferric subsulfate) can be very useful to control the bleeding. Only rarely, the biopsy defect requires suturing.

The simplest method is biopsy with cervical biopsy forceps. The bleeding is minimal and can be stopped by simple pressure or application of Monsel's solution (Figure 4a-c). Ulcerative lesions and very thick lesions should be completely excised to rule out focal invasion (excision biopsy). An elliptical excision is made with scalpel and the wound is closed by 2/0 or 3/0 vicryl sutures. After the biopsy, the specimen should be put on absorbent paper with the dermal side down, facing the epithelial side upwards. Formalin (10%) is usually used as a fixative. It is very important to orient the specimen properly, to avoid tangential sections, which may cause difficulties in histological interpretation.

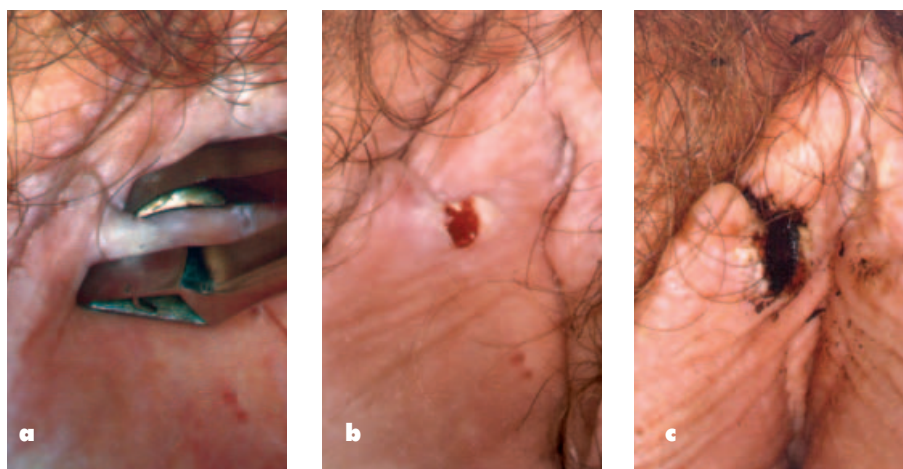


Figure 4. Vulvar biopsy using biopsy forceps. a) Biopsy of the vulva with biopsy forceps. b) Biopsy site. c) Biopsy site after application of Monsel's solution.

## DOCUMENTATION OF VULVAR FINDINGS

The colposcopic findings on the vulva should be precisely documented. A schematic drawing in the patient's record has sufficed for many years. For this purpose, the simplified scheme of the vulva which presents labia majora, both sides of labia minora, vestibule, perineum and anus is sufficient. Exact localization of any finding should be marked in this diagram (Figure 5). More objective documentation of colposcopic images may be achieved by photographic camera attached to the colpo-

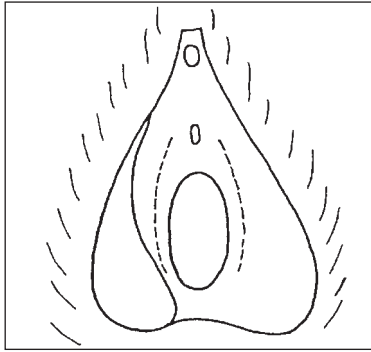


Figure 5. Diagram for vulvoscopic report

ing for objective documentation of vulvar findings, too (3).

### NORMAL VULVAR FINDINGS

Features of hair-bearing skin on the labia majora are similar to the other non-genital areas of skin. Normal skin is smooth, slightly pigmented, covered by hair and contains skin appendages, which are sometimes clearly visible. Normal mucosa of the labia minor and vestibule is smooth and pink in childhood, whereas extensive or localized micropapillary or villiform pattern is seen during the reproductive age (Figure 6). Numerous rugae and papillae are present in the labia minora and near the hymenal ring. These occasionally fuse and coalesce and can be misinterpreted as representing human papillomavirus (HPV) infection (4). The skin of the labia minora may be pigmented, the pigmentation becoming obvious during adolescence. Smooth, 1-2 mm large, white or yellow papules may be present especially in upper and inner parts of the labia majora as well as in the labia minora. These tiny elevations are referred to as



Figure 6. Normal mucosa of the labia minor and vestibule

Fordyce spots and represent normal sebaceous glands, which in this area open directly to the surface, while in hair-bearing areas they open to the hair follicles. Openings of small vestibular glands can also be seen occasionally.

After the menopause, in the absence of oestrogen, the vulvar skin becomes pale, thin and dry, resulting in pruritus and general irritation. After the application of acetic acid, it whitens. This is associated with a thinning of labial hair due to the loss of follicles with increasing age and reduction of pigmentation.

scope or by extending the colposcope with a video camera, an on-line monitor and video printer. Recent advances in computer technology using digital colour imaging colposcopy system, up to now applied for the examination of the cervix, seems to be promising

It is important to study the “normal conditions” of the vulva, because mild vulvar changes are classic examples of conditions that are often “over-treated” (5). Normal colposcopic appearance of the vulva includes 1. acetowhite areas, and 2. filamentous lesions.

### ACETOWHITE AREAS

Following the application of acetic acid, a variable extent of acetowhiteness develops proximally to the Heart's line (the border of non-keratinized vestibular epithelium and thin keratinized epithelium of labia minor). Usually, it spreads a few millimeters lateral to the vulvo-vaginal line on the medial aspect of labia minora, but not extending to the fourchette. The vulvo-vaginal line is defined by the presence of the hymen or its remnants. At that point, going upwards, begins the glycogen rich, non-keratinized vaginal epithelium.

The characteristic appearance of this acetowhite area has the shape of a horse-shoe (Figure 7). It is not associable with HPV infection but represents a variant of normal epithelium, maybe caused by constant scratching and rubbing (6). Usually, it does not have clinical significance. At the present time, the degree of acetowhiteness and its relationship to vulvar disorders has not been properly determined (7). In any case,



Figure 7. Normal acetowhite change (horse-shoe) around the introitus

if intensive acetowhiteness is present, the examination and, if necessary, biopsy should exclude HPV and VIN changes particularly if the lesion extends to vaginal epithelium.

### PHYSIOLOGICAL HYPERPLASIA (VESTIBULAR PAPPILOMATOSIS)

Vestibular papillomatosis was first described nearly two decades ago. At that time, the condition was thought to be infrequent showing the prevalence of 1%. Today, these changes can be seen more often (8). Other names for this condition include pseudo-condylomatosis, pruritic squamous papillomatosis, benign squamous papillomatosis, hirsutes papillares vulvae, vestibular micropapillomatosis and others. There is no general agreement in terms of aetiology of vestibular papillomatosis. In the beginning, it was considered a normal anatomic variant. Later the changes were ascribed to HPV infection, because of their similarity to HPV infection or even VIN (9). However, numerous studies did not confirm the relationship between vestibular papillomatosis and the presence of HPV infection. It was shown that HPV DNA was detected in only 6.9% of such cases, which

is equal to the prevalence of HPV DNA in women with normal vulvar mucosa (10). The prevalence of HPV infection in these lesions is too low to be considered causal (11).

Vestibular papillae are small excrescences, quite regularly and symmetrically distributed over the vestibular mucosa. Sometimes their distribution is linear along the inner surface of the labia minora, vestibule and fourchette. In sexually active women, they can occupy the entire surrounding of the vestibule (12). They are in essence projections of connective tissue covered by a normal epithelium (*Figure 8*). In the majority of cases, they are occasional findings and asymptomatic, but some patients do complain of pruritus, vulvodynia, superficial dyspareunia or postcoital irritation. More often, they are noticed in patients taking oral contraceptives, but they also can be seen in girls who have never had sexual intercourse.

Vestibular papillae present as numerous, smooth, white, soft finger-like projections which can be several millimeters long. Therefore the area where they are present looks pearly. Sometimes, they can extend to 6-8 mm. These papillae can be distinguished from HPV induced lesions on the basis of their regular shape and distribution, uniform colour, soft consistency and lack of tendency to fuse (*Figure 9*).

A follow-up of patients with vestibular papillomatosis for more than 18 months showed that both the distribution and appearance of these papillae remained unchanged, and the male partners did not show HPV related lesions (13). Despite the uncertainties regarding the aetiology of vestibular papillomatosis, all authors agree that patients with symmetrically distributed, vestibular papillae that have been present for a long time should not be treated, but observed.

### CHARACTERISTICS OF ABNORMAL VULVAR FINDINGS

Keratinization interferes to a greater or lesser degree with the filter effect upon which the grading of colposcopic images

on the cervix and vagina depend. Keratin is opaque, making evaluation of thickness of the affected vulvar epithelium difficult. Therefore, the prediction of histological diagnosis, which is often possible on the cervix and vagina, is much more difficult for vulvar lesions.

Until recently, there has been no attempt to classify colposcopic findings on the vulva. With trying to classify vulvar findings it is possible to use the same descriptive process for the vulva as for the cervix. The most appropriate for this purpose remains the Coppleson and Pixley's classification of colposcopic findings of the vulva based on a few important characteristics of the lesions: 1. colour: normal, white, acetowhite, red, brown, and other pigmentation, 2. blood vessels: absent, punctation, mosaic, and atypical vessels, 3. surface configuration flat, raised, micropapillary, microcondilomatous, villiform, papular, and hyperkeratotic (leukoplakia), and 4. topography: unifocal, multifocal, multisited, e.g. perineal, urethral, vaginal, and cervical (7).

Combining particular features of the vulvar lesions can help colposcopic predictions of its histological nature, but this is much less reliable than colposcopic grading of cervical lesions (7).

### COLOUR

The principal feature of vulvar lesion, from a colposcopic point of view, is the colour. This is probably the most informative distinction of the lesion. Colour changes are common in the vulvar epithelium. They are easily visible to the naked eye. Colour of vulvar lesions varies from white to black. It will depend upon pigmentation, vascularity of the dermis and the thickness of the overlying epithelium. Including all the varieties in between, vulvar lesions can basically be: 1. white, 2. red and 3. dark.

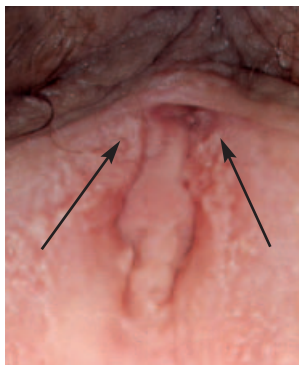
### WHITE LESIONS

White lesions are not always neoplastic. Superficial keratin layer, any degree of depigmentation, relative avascularity of tissue and reaction to acetic acid contribute to the development of white colour.

When superficial keratin undergoes maceration due to the increased moisture of the vulvar area, it turns opaque and its colour becomes white or grey. The thicker the keratin layer is, the more the effect is expressed (*Figure 10*).



*Figure 8.* Vestibular papillae. *Insertion* Higher magnification of papillae



*Figure 9.* Vestibular papillomatosis (arrows)



*Figure 10.* White lesion

Depigmentation is loss or absence of melanin pigmentation. It develops if melanocytes in the basal layer are lost or destroyed or when these cells lose their ability to produce melanin (vitiligo). Localized white lesions may result from transient loss of pigment in a residual scar after healing of an ulcer (leukoderma).

A relative decrease in vascularity appears when superficial blood vessels become narrow and the distance between them increases, which happens in Lichen sclerosus. Histologically, white lesions may present 1. non-neoplastic epithelial disorders, 2. HPV infection, and 3. VIN.

To differentiate VIN from other white lesions, which appear on the vulva, a biopsy should be taken.

### RED LESIONS

Normal colouring of the skin is the result of light reflection from the superficial blood vessels situated in the dermis. As light traverses through the epidermis, which lies above the dermis, a decrease in the thickness of the epithelium or any increase in the vascularity gives a red appearance to the skin



Figure 11. Red lesion on the vulva

(Figure 11). A red lesion results from the thinning or ulceration of the epidermis, the vasodilatation of an inflammation or an immune response or the neovascularisation of neoplasia (14).

Many of these red lesions are symptomatic and are accompanied with pruritus, pain and occasional bleeding due to fragility of superficial capillaries. Diffuse redness is usually associated with benign processes (infections and different dermatoses), while each localized red lesion may be suspicious of neoplasia.

Red lesions may present local immune response or inflammatory reaction in conditions such as 1. inflammation (dermatitis, eczema), 2. infection (candidiasis, tinea cruris, folliculitis), 3. dermatosis (psoriasis, intertrigo, Lichen planus) 4. neoplasia (VIN, Paget's disease, cancer).

### DARK LESIONS

Dark lesions are due to an increased amount or concentration of melanin or blood pigment (Figure 12). Vulvar lesions appear dark if melanin is present intraepithelially and/or intradermally. In these lesions, synthesis of melanin is amplified in epidermal melanocytes. The excess of melanin is afterwards ejected in the papillary dermis wherefrom it is taken by melanophages by a process of fagocytosis. This me-



Figure 12.  
Dark lesion  
on the vulva

chanism is known as “melanin incontinence” and produces a pigmented appearance of many VIN lesions (15). Pigmentation of vulvar skin may occur after trauma. Vulvar skin may darken following the use of oestrogen cream applied to the vulva and vagina for the treatment of a vaginitis or after oral contraceptive use.

Dark lesions may present: 1. pigmentation disorders – hyperpigmentation, 2. nevi, lentigo, seborrheic keratosis, 3. VIN and 4. malignant melanoma.

Vulvar lesions may show any other variety of colour. Particularly recognizable are lesions which originate from vascular tissue such as angiomas or choriocarcinomas, which are typically violet. Necrotic tissue usually has yellow colouring.

### VASCULAR PATTERN

It has been pointed out that a vascular pattern can not be easily seen on surfaces covered by keratinized skin, particularly on hair-bearing areas. If punctations and mosaic are present, intravascular distance (the size of mosaic fields or distance between punctations) is evaluated in the same manner as when colposcopic grading of cervical lesions is concerned (Figure 13). Clearly visible atypical vessels are usually suggestive to invasive cancer (Figure 14).



Figure 13. Atypical vascular pattern  
on the vulva



Figure 14. Atypical vascular pattern:  
invasive vulva cancer

## SURFACE CONFIGURATION

Whatever the surface of the lesion is, all vulvar lesions can be regarded in relation to the level of the surrounding skin. They can be situated: 1. below the level of surrounding skin (erosions and ulcerations), 2. in the skin (macula, acetowhite lesions, pigmentation disorders), and 3. raised above the surrounding skin (proliferative lesions, vesicles, papulae, pustule, leukoplakia).

Erosions and ulcerations are below the level of the surrounding epithelium. They are typical findings for some infections and dermatoses such as herpes infection, syphilis, Behçet's or Crohn's disease and other ulcerative and bullous skin disorders. Ulcerative lesions may suggest a granulomatous sexually transmitted disease or cancer.

Lesions in the level of skin are usually part of dermatological conditions such as allergic reactions or pigmentation disorders. Subclinical HPV infection and VIN can also be localized in the thickness of epithelium only, particularly if present on the skin of labia minora or vestibular epithelium. In these cases, they are recognized by the change in colour.

The majority of lesions are raised above the surrounding skin. HPV infections, VIN and invasive cancer usually present as raised lesions. Other conditions like benign tumours, tumour-like conditions and dermatologic diseases or leukoplakia of any cause, should be excluded by biopsy. Superficial aspect of all these lesions wherever they are situated can be smooth (hemispheric or flat) or irregular (micropapillary, microcondilomatous, villiform).

## TOPOGRAPHY

Vulvar lesions can be sited on the skin (hair-bearing, or non-hair-bearing) and mucosa. Many vulvar lesions are multisited. Examine all sites of vulva! Vulvar lesions may be 1. unifocal, and 2. multifocal. Majority of the VIN changes are multifocal. Look for multifocal changes!

Some of recent colposcopic classifications of vulvar findings such as the one recently proposed by *Audisio et al.* (16), define a variety of vulvar lesions very precisely. Although they are very useful, for practical purposes, abnormal colposcopic appearances in the vulva may be summarized as follows: 1. single or multifocal white, red or pigmented lesions apparent before the application of acetic acid, 2. acetowhite change appearing after prolonged soaking of the skin using acetic acid-soaked swabs, and 3. abnormal vessel patterns which may be seen but are less common, probably due to the masking effect of keratinization.

On the basis of the macroscopical aspect and the distribution of vulvar changes it is not possible to distinguish between various types of vulvar lesions. Distinction based on the charac-

teristics of vulvar lesions is not indicative of histology. Therefore the rule is that for definite diagnosis of vulvar lesion a biopsy should be performed. On the other hand, vulvoscopy can exactly localize the lesion, and although not having the important role in the presence of a clinically evident lesion, it is very useful in directing the biopsy site and mapping the limits of the lesion at the time of excision.

## CLASSIFICATION OF VULVAR LESIONS

Vulvar pathology is a concern of several specialities, which reflects the complex morphology, and the variety of functions through the life cycle of women. The vulva is the region where numerous local or systemic diseases can be found. The spectrum of abnormalities that can affect the vulva ranges from infections, inflammatory conditions and dermatoses, similar to those encountered in extra-genital skin, to vulvar intraepithelial neoplasia and invasive cancer. The last decade has witnessed significant advances in the study of vulvar pathology, making the terminology of vulvar disease even more confusing than it has already been over the years.

In the attempt to unify the nomenclature for the variety of vulvar diseases, the International Society for the Study of Vulvar Disease (ISSVD), a multidisciplinary association which among the other specialities, includes dermatologists,

*Table 1.* International Society for the Study of Vulvar Diseases (ISSVD) and International Society of Gynaecological Pathologists (ISGP) classification

### A. NON-NEOPLASTIC EPITHELIAL DISORDERS OF VULVAR SKIN AND MUCOSA

Lichen sclerosus (LS)

Squamous cell hyperplasia (formerly hyperplastic dystrophy)

Other dermatoses

[Mixed epithelial disorders may occur. In such cases it is recommended that both conditions should be reported. For example: LS with associated squamous cell hyperplasia (formerly classified as mixed dystrophy) should be reported as LS and squamous cell hyperplasia. Squamous cell hyperplasia with associated vulvar intraepithelial neoplasia (VIN) (formerly hyperplastic dystrophy with atypia) should be diagnosed as VIN. Squamous cell hyperplasia is used for those instances in which the hyperplasia is not attributable to another cause. Specific lesions or dermatoses involving the vulva (e.g. psoriasis, Lichen planus, Lichen simplex chronicus, candida infection, condyloma acuminata) may include squamous cell hyperplasia but should be diagnosed specifically and excluded from this category.]

### B. VULVAR INTRAEPITHELIAL NEOPLASIA (VIN)

Squamous vulvar intraepithelial neoplasia

VIN 1 (mild dysplasia)

VIN 2 (moderate dysplasia)

VIN 3 (severe dysplasia or carcinoma in situ)

VIN 3 - carcinoma in situ differentiated type

Non-squamous vulvar intraepithelial neoplasia

Paget's disease

Melanoma in situ



pathologists and gynaecologists, proposed, in 1990, the system for classification of vulvar lesions. This classification was supplemented in 1993 and still seems to be the most appropriate one (17). Their recommended terminology distinguishes between non-neoplastic skin disorders and VIN (*Table 1*).

ISSVD introduced the term “non-neoplastic epithelial disorders of skin and mucosa” to include Lichen sclerosus, squamous cell hyperplasia and other dermatoses and VIN to include atypias and carcinoma in situ. However, the term “non-neoplastic epithelial disorder” causes another confusion since

*Table 2.* Revised ISSVD classification of non-neoplastic vulvar disorders

INFECTIONS	Granulomatous disorders	Deficiency
Parasitic, e.g. pediculosis, scabies	Non-infectious	Physiological
Protozoal, e.g. amoebiasis	Sarcoidosis	Lactation
Viral, e.g. herpes virus infection, condyloma acuminatum	Crohn's disease	Postmenopausal
Bacterial	(Hidradenitis suppurativa)	Others
Fungal, e.g. candidiasis, dermatophytosis	Others	Iatrogenic
Others	Infectious	
	Tuberculosis	Androgen
INFLAMMATORY SKIN DISEASE	Granuloma inguinale	Excess
Spongiotic disorders	Others	Physiological
Contact dermatitis		Iatrogenic
- Irritant	Vesiculitis or related inflammatory disorders	ULCERS AND EROSIONS
- Allergic	Leukocytoclastic	(diseases that ulcerate and/or erode are listed according to histological findings)
Atopic dermatitis (acute and chronic)	Urticaria	Trauma
(Seborrhoeic dermatitis)	Aphthous ulcer	Obstetrical
Others	Lymphoedema	Surgical
Psoriasiform disorders	Behcet's disease	Sexual
Psoriasis	Pyoderma gangrenosa	Accidental
Lichenification (Lichen simplex)*	(Fixed drug eruption)	Others (include fissures of the fossa navicularis)
Atopic dermatitis (chronic)	(Erythema multiforme)	
Seborrhoeic dermatitis	(Stevens-Johnson syndrome)	
Others	Others	
Lichenoid disorders		DISORDERS OF PIGMENTATION
Lichen sclerosus	SKIN APPENDAGE DISORDERS	Hyperpigmentation
Lichen planus	Hidradenitis suppurativa	Melanin
Fixed drug eruption	Fox-Fordyce disease	Lentigo
Plasma cell vulvitis	Disorders of sweating	Melanosis vulvae
Lichenoid reaction, not otherwise specified	Others	(Postinflammatory hyperpigmentation)
(focal or diffuse)		Haemosiderin
Lupus erythematosus	HORMONAL DISORDERS	(Postinflammatory hyperpigmentation)
Others	Oestrogen	Vitiligo
Vesicobullous disorders	Excess	Others
Pemphigoid	Precocious puberty	Hypopigmentation
Pemphigus	Others	Vitiligo
Erythema multiforme		Postinflammatory hypopigmentation
Stevens-Johnson syndrome		Others
Others		

This revised classification replaces the ISSVD classification of non-neoplastic epithelial disorders. It is not intended to be a comprehensive listing of all known dermatological or pathological disorders that may involve vulva or vagina, but to include the more common disorders that involve the vulva.

What has been interpreted as vulvar vestibular inflammation may represent, in some cases, findings considered as within normal.

\* The term “lichenification” encompasses the former ISSVD terms of “squamous cell hyperplasia” and “hyperplastic dystrophy”. Lichenification encompasses the term “lichen simplex” (lichen simplex chronicus)

Maclean AB. Are “non-neoplastic” disorders of the vulva premalignant? In: *Cancer and Pre-cancer of the Vulva*, Luesley DM (ed). Arnold, London, 2000:74-85.

it may coexist with neoplastic lesions. Therefore, the Terminology Committee of the ISSVD modified it in November 1997. The “non-neoplastic inflammatory disorders of the vulva include the more common disorders that involve vulva (Table 2). However, vulvar pathology is more complex, includes many other conditions and generally may be divided into: 1. traumatic lesions, 2. disorders of pigmentation, 3. chronic unexplained vulvar pain syndromes, 4. infections, 5. dermatoses (ISSVD: non-neoplastic epithelial disorders), 6. tumour-like lesions, 7. benign tumours, 8. intraepithelial neoplasia (ISSVD: neoplastic epithelial disorders – VIN and non-squamous intraepithelial neoplasia) and 9. invasive neoplasia.

These conditions are associated with a variety of appearances and, in some instances, may mimic the appearance of cancer and precancer. Realizing the complexity of vulvar pathology, only a selected few will be addressed, because of their importance to the clinician.

### TRAUMATIC LESIONS

Traumatic lesions of the vulva may be caused by physical, chemical and radiation injury. Physical injuries to the vulva include accidental injuries, female genital mutilation and the lesions resulting from sexual assault. This type of vulvar damage is usually easily recognized presenting as oedema, haematoma (Figure 15), lacerations or scars. Chemical and radiation injuries cause severe necrotic changes, which usually result in intensive scarring. From a colposcopic point of view, the injuries caused by sexual assault and the changes resulting from radiation deserve special attention.



Figure 15.  
Haematoma of  
the vulva

### SEXUAL ASSAULT

Sexual assault (rape) is a forensic term characterizing sexual activity perpetrated against the will of the victim. The question of consent will ultimately remain with the court. Nevertheless, obtaining corroborative physical data supporting the history in a time frame consistent with the alleged sexual activity is an important part of the medical assessment (18). The outcome of this assessment depends on accurate examination. The physician must accurately obtain the details of the assault, take a detailed gynaecological history and, above all, perform structured and skillful physical examination. The

identification of the location, nature and the extent of external trauma must be known and, if possible, all visible lesions should be photographed.

While it is clear that a physical examination is an important element in patient management because the findings of that examination can be a crucial factor in the corroboration of rape, conventional protocols have historically yielded positive genital findings in only 10-30% of cases (19-20). Colposcopic magnification might maximize visualization of genital findings. The clarity afforded by colposcopic magnification will also allow further characterization of genital changes associated with rape. With greater frequency and reliability, colposcopy can identify physical findings in rape victims examined within 48 hours after the event. This is making colposcopy and colpophotography particularly important in clinico-forensic diagnostics and reliable method for documentation of findings.

Genital examination should begin by gross inspection of the vulva with special attention to the introitus and hymen, perineum and approximately the distal 2 cm of the vagina. Meticulous inspection of these fields should be performed and a careful diagram made. This is followed by colposcopic assessment of the same area at 15x magnification. Both white light and green filter should be used. A speculum should be inserted into the vagina, and the vagina and cervix carefully examined. After all forensic smears are taken, toluidin blue is applied to the fourchette. This area is then reinspected grossly and colposcopically. Lacerations that expose deeper dermis will bind toluidin blue increasing the percentage of visible lacerations from 4.16 to 50.83% (21). Toluidin blue is not of much use in areas of superficial injury or the ones which began to reepithelialize.

If examination is performed 6 hours after intercourse, micro-abrasions and, in 10%, other signs of trauma (increased vascularity, teleangiectasiae, broken capillaries and oedema) may be seen, but these changes are not localized (22). In contrast to this, rape victims typically have injuries of the posterior fourchette. This is the anatomical site of attachment to the perineal body and hence the point of greatest stress when force is applied. Besides this, it is the point of first contact between the penis and vagina and resulting trauma may be characterized as acute mounting injury (22).

Predominantly, injuries are situated at 3, 6 and 9 o'clock on the posterior fourchette and concentrated to the area between 5 and 7 o'clock. They include lacerations, abrasions, ecchymoses and swelling (Figure 16). Bite marks, rape burns or fingernail scratches may be present on the labia majora and adjacent structures. Abrasive injuries can be seen on the medial aspect of the labia minora. Usually lacerations are located at 6 o'clock.

They often extend tearing fossa navicularis and the hymen. The rugal folds of the posterior fourchette make genital trauma difficult to see by gross visualization alone.

Colposcopically it is not difficult to differentiate the physiological folds from old, fine scars and clearly visible new tears. It is also possible to see fine haematomas in between hymenal folds and also small fissures and abrasions which could not be noticed by the naked eye. Even if the hymen was not torn, the break in integrity of the hymenal capillary system may be seen, if the blunt power was not sufficiently strong to tear the hymen (*Figure 17*). During the first 24-48 hours, small haematoma in the basis of hymen may be seen. Haematoma may be multiple if the system is broken in a few points. After 48 hours, these haematomas disappear.



*Figure 16.* Typical injury as a result of sexual assault

Up to, in average 25 days, acute injury heals. Hymenal tears do not reunite, epithelization is complete, and no scars can be seen except in the patient who required suture. The documentation of the healing process is an important part of the forensic assessment. It links the traumatic event to the injuries observed, establishing a time frame reliability associated with the injury. Prompt assessment of the rape victim by a multidisciplinary team that incorporates medical examination with colposcopy may be the best way of collecting and documenting the forensic evidence in rape cases.



*Figure 17.* Subethelial haemorrhagia in the hymenal ring with tear

### RADIATION INJURIES

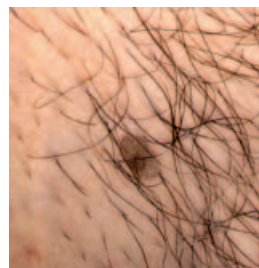
Acute and late injuries of the vulva and vagina are frequent and potentially serious complications of the radiotherapy of gynaecological tumours. Vulvar tissue is sensitive to X-rays and necrotic ulcers may result. Necrotic patches later detach and adhesions of denuded stroma, proliferation of connective tissue and induration may take place (*Figure 18*). Afterwards, mucosa is smooth, thin, yellow to pale pink and fragile. Tissue is not elastic. Typical teleangiectasiae, atrophy and pigmentation can be seen. Fields of avascular necrosis may persist for a long time, up to 6 months. After stabilization of the acute phase, late necrosis similar to leukoplakia with dense small



*Figure 18.* Radiation necrosis



*Figure 19.* Hyperpigmentation



*Figure 20.* Lentigo on the vulva



*Figure 21.* Nevus on the vulva

network vascularisation, as well as, lesions suspicious to recurrence occur. Such tissue is recognized to be prone to the development of carcinoma. Hygiene measures and topical application of antimicrobial or granulation stimulating substances, which is mostly based on long-standing clinical experience, are the principles of the treatment of acute reactions of vulva and vagina. The topical use of oestrogen, which promotes proliferation of the epithelium, is generally described in connection with treatment and prophylaxis of late radiation injuries (23).

### PIGMENTATION DISORDERS

Pigmentation disorders include hyperpigmentation and hypopigmentation. Hyperpigmentation is caused by the presence of haemosiderin and melanin in the skin or as a skin reaction after taking some medicaments (fixed drug eruption) (*Figure 19*). Marked diffuse macular hyperpigmentation may be the result of a post-inflammatory condition. Lentigo is a benign pigmented proliferation of the epidermal or mucous membrane melanocytes.

It is smooth, flat, non-inflammatory, single or multiple patch, light to medium brown that usually appears on the labia minora and around vestibule (*Figure 20*). Nevus is a single, isolated, slightly prominent lesion located on the skin or mucosa (*Figure 21*). Acanthosis nigricans is rare and a specific dermatosis which can occur either alone or as a part of some endocrinologic syndromes. It is usually associated with internal malignancy, most often adenocarcinoma and less frequently lymphoma or epithelial cancer. Although the lesions can be found on other parts of the skin or mucosal surfaces, most often they

Figure 22. Acanthosis nigricans

affect the genital region. They are dark and, at the first they have a velvet-like surface, which later becomes warty (Figure 22). In less severe cases, it may clinically be confused with the condition of pseudoacanthosis nigricans – dark, thickened areas of skin in folds, often associated with skin tags which appear in obese individuals and disappear after weight loss (24). Vitiligo is complete depigmentation of limited, well defined and usually symmetric areas of the skin, which is otherwise normal. It appears because the loss of number or absence of melanocytes (Figure 23).



Figure 23. Vulvar vitiligo

### UNEXPLAINED CHRONIC VULVAR PAIN SYNDROMES

The most puzzling problem in gynaecology is the unexplained chronic vulvar pain. For practitioners the most important ones are dyesthetic (“essential”) vulvodynia and vestibulitis. They will be briefly mentioned because of their clinical importance and absence of any specific gross or colposcopic findings. The aetiology of these conditions has not been understood yet. The patients are usually depressed, significantly more likely to be anxious and somatizing, hypochondriacal, tending to consult more doctors about their symptoms and to have symptoms that interfered more seriously with their sexual functioning than in women with other forms of vulvar pathology (25). On the other hand, doctors make the common mistake of prescribing drugs, especially topical preparations of steroids, antifungal creams or antibiotics, without proper diagnosis. In some patients, the current complaint could in fact be related to inappropriate medication, which might have intensified vulvar discomfort or pain.

### VULVODYNIA

Non-provoked intractable idiopathic pain that has been designated as dyesthetic (“essential”) vulvodynia. It is considered a unique syndrome (26). The initial parameters of vulvodynia have been described long ago: 1. persistent symptoms of long-standing duration, 2. lack of demonstrable pathology, 3. sexual inactivity as a direct result of symptoms, 4. unsuccessful consultation with multiple physicians, 5. “allergy” to many

common vaginal preparations, 6. reluctance to accept the suggestion of a psychopathologic cause, 7. emotional lability and dependency (27).

### VESTIBULITIS

Vulvar vestibulitis syndrome (intorital, vestibular dyspareunia) is another frequently seen vulvar pain syndrome. It is the condition of chronic, intractable provoked pain, appearing during sexual intercourse or with any vestibular contact. It may develop at any age, but it is seen most commonly in young, sexually active women. It has three distinctive criteria: 1. severe pain on vestibular touch or attempted vaginal entry, 2. tenderness to pressure localized within the vulvar vestibule, 3. physical findings confined to vestibular erythema (28).

The erythema seen in this syndrome may be diffuse or focal, and may be localized around the orifices of the major (Bartholin’s, Skene’s or periurethral) or minor vestibular glands or at the fourchette (Figure 24) (29). The presence of any characteristic changes in vestibular tissue has been doubted because it has been shown that in healthy asymptomatic women the same physiological changes are present (30). At present, vestibulitis or VVDS (vaginal vestibulitis dyspareunia syndrome) is considered to be a consequence of some process which has not yet been discovered (31). Optimal management of these

conditions should include a multidisciplinary medical approach, as well as, a sympathetic and careful approach which will make the patients feel not only that their disorder is recognized, but also respected.



Figure 24. Vestibulitis



Figure 25. Mesonephric cyst of the vulva

### TUMOUR-LIKE LESIONS

Tumour like lesions include: ectopic tissues (breast and salivary), nodular fasciitis, desmoid tumour, verruciform xantoma, endometrioma and cysts. Endometrioma usually arise following episiotomy and surgical wounds. It is blue to purple, cystic, ill-defined, firm or fluctuant mass which shows cyclical swelling and causes discomfort. Cysts can arise in development remnants (mesonephric) (Figure 25), due to

blockage of the gland ducts (retention cysts) (Figure 26) or an epithelial inclusion.

## BENIGN TUMOURS OF THE VULVA

Benign tumours of the vulva, although relatively uncommon, are often referred to dermatologists for evaluation and treatment. The clinical features of benign tumours may overlap with malignant neoplasms, and therefore, a biopsy is often necessary to make a definitive diagnosis (32). Benign tumours of the vulva may arise from both epithelium or underlying stroma. Epithelial tumours comprise of a group of common skin changes, which range from small to rather large formations and sometimes may resemble malignant lesions.

### SQUAMOUS PAPILLOMA

Squamous papillomas are solitary lesions of the middle age and elderly. Aetiology is unknown. They are finger-like projections consisting of stromal fibro-vascular tissue covered by focally acanthotic and hyperkeratotic epidermis (Figure 27). There is no cellular atypia and this lesion is not regarded as having any malignant potential.

### FIBROEPITHELIAL POLYP (FIBROEPITHELIOMA, SKIN TAG)

A fibroepithelial polyp is a common vulvar lesion, usually solitary, soft, sometimes with wrinkled surface. It consists of connective tissue covered by squamous epithelium, which can be atrophic or mildly acanthotic and hyperkeratotic (Figure 28). The lesion is usually of small polypoidal nodule (a few millimeters to a few centimeters), which may sometimes attain a striking size and appear pedunculated. The surface is vulnerable, oily and granulated or verrucous and the colour may be similar or darker than the surrounding skin, ranging from pale brown to black (33). Sometimes, due to increased pigmentation, they resemble malignant melanomas.



Figure 26. Retention cyst on the vulva



Figure 27. Squamous papilloma of the vulva



Figure 28. Fibroepithelial polyp on the vulva

### BASAL CELL PAPILLOMA (SEBORRHOIC KERATOSIS)

These tumours occur on any part of the body, most commonly after middle age. They appear single or in corps. Frequently, they cause irritation and occasionally pain. Their morphology is exophytic and sometimes papular. They appear as pale brown to black, soft, friable, greasy, granular, velvety or verrucous, flattened, rather irregular, stuck on plaques, which vary in size from a few millimeters to several centimeters (Figure 29) (34). In some instances due to their heavily pigmentation, they may be clinically confused with malignant melanomas.



Figure 29. Seborrheic keratosis on the vulva

### KERATOACANTHOMA

This is a benign squamous skin lesion that usually appears in middle and older age on the areas exposed to sun. When it appears on vulva, external surface of labia majora is the most affected site. Clinically and histologically it resembles planocellular carcinoma. The lesions are characteristic: firm, round or oval, flesh coloured or red. In a few weeks, they develop into a well-demarcated hemispherical nodule with central keratin-plugged crater, 1-2 cm in diameter (35). They resemble giant mollusca. Its clinical course may be fast and alarming growth can be seen over a few weeks. Typically, the lesion continues to grow up to 6 months and then regresses spontaneously leaving a small depression scar. They rarely display metastatic properties but even then, their behaviour is not malignant and metastases have never been described. Treatment is complete excision.

### MESENCHYMAL TUMOURS

Benign tumours derived from mesenchymal tissues are usually massive, between 2-8 cm and, occasionally, they can attain, huge size. They appear either as subcutaneous nodules or pedunculated (due to gravitation effects), sometimes superficially ulcerated masses. Most often they originate from labia majora, but some large benign tumours have been discovered on the clitoris. They may originate from smooth or striated muscle (leiomyoma or rhabdomyoma), fibrous tissue (fibroma), fat (lipoma), or they may have vascular (haemangioma), lymphatic (lymphangioma) or neural origin (neurolemoma). The most common are vascular benign tumours.

### HAEMANGIOMA

Haemangioma is a benign formation originating from vascular tissue which usually occurs in childhood. Clinically significant vulvar haemangiomas are rare and only a small number

of these tumours are reported in literature. The majority of these tumours remain clinically undetected, but, in some instances, they may attain noticeable size (Figure 30). haemangiomas may be localized on the clitoris, occasionally resulting in clitoromegaly. Such conditions may be misleading, falsely interpreted as intersexuality or congenital adrenal hyperplasia (Figure 31).

### ANGIOKERATOMA

Most common of all vascular tumours are angiokeratomas and the vulva is a predilection site for their occurrence. They are usually seen in women between 20–40 years. The vast majority arise in the labia majora. Usually, they are symptomatic, but may cause pruritus and bleed. Angiokeratomas are solitary formations but they can be multiple as well, presented by more than 20 separate lesions (36). They measure from 2-10 mm and they can have a papular, globular or warty appearance (Figure 32). In the early stages they are usually red but later their colour change to brown or black. When angiokeratoma is presented by black warty change, it can resemble malignant melanoma. The excision, which is at the same time therapeutic, confirms the diagnosis.



Figure 30. Vulvar haemangiomas

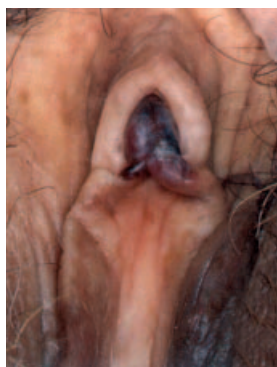


Figure 31. Haemangioma of the clitoris



Figure 32. Angiokeratoma on the vulva

## INFECTIONS OF THE VULVA

Vulvar skin provides a warm, moist environment exposed to urinary and fecal soiling. Although keratinized epithelium protects well against infection, there are factors that make this region prone to infection. These include the presence of normal commensals (staphylococci, diphtheroid bacilli), warmth and humidity of the region and normal activity of numerous sebaceous glands.

Infections frequently cause problem in clinical practice. Each woman has at least once in her life time a vulvar infection. Infections that affect the vulva may be caused by many dif-

ferent microorganisms ranging from parasites to viruses. In many instances, vulvar infections produce lesions which are difficult to distinguish from true neoplastic conditions. Since the problem of infective vulvar diseases deserves much more attention in regards of epidemiology, diagnosis and treatment, we will discuss only those, that are most frequent or produce most typical clinical manifestations which should be properly recognized.

### INFESTATIONS (ECTOPARASITES, NEMATODES AND PROTOZOA)

#### PEDICULOSIS PUBIS

CAUSATIVE AGENT *Phthirus pubis* (the crab louse).

TRANSMISSION Sexual contact.

INCUBATION 30 days.

CLINICAL APPEARANCE Pubic, perineal and perianal regions are most affected. Intensive itching is present. Typical skin lesion is “macula cerulea”, bluish-grey macule that rapidly fade. Minute pale-brown insects and their ova may be seen attached to terminal hair shafts.

THERAPY 0,5% malathion lotion.

#### SCABIES

CAUSATIVE AGENT *Sarcoptes scabiei*.

TRANSMISSION Close and fairly prolonged direct contact or indirect transmission by contaminated clothes.

INCUBATION 12-30 days.

CLINICAL APPEARANCE Intractable itching and excoriation of the skin surface in the vicinity of minute skin burrows where parasites have deposited ova.

THERAPY Permethrin 5% creme.

#### ENTEROBIASIS (THE THREADWORM)

CAUSATIVE AGENT *Enterobius vermicularis*.

TRANSMISSION Ingestion of ova through dirty skin, food and water.

CLINICAL APPEARANCE Nocturnal perianal itching causing perianal excoriations which are easily visible. Vulvar irritation and vulvovaginitis may occur. Threadworms are 3-12 mm long and may be found around the anus or between the labia.

THERAPY Piperazine salts.

**AMOEBIASIS**

**CAUSATIVE AGENT** Entamoeba histolytica.

**TRANSMISSION** Direct contact or via flies, food and water.

**INCUBATION** 20 days (from 4 days to several months).

**CLINICAL APPEARANCE** Most lesions begin as cutaneous abscess which rupture and form painful, serpiginous ulcer with a sloughing base. They may also be present as wart-like lesions. The perineum, vulva and the cervix may be affected as well as the local glands (37). These lesions are usually due to a direct extension of intestinal disease which is already present but some are believed to arise after the inoculation of the organism through sexual contact.

**THERAPY** Metronidazole.

**MYCOTIC INFECTIONS****VULVO-VAGINAL CANDIDIASIS**

**CAUSATIVE AGENT** Candida species, most frequently candida albicans.

**GENERAL CONSIDERATIONS** These infections are common and it is thought that 75% women at least once in their life time have symptomatic candidiasis. Forty-five percent of these women are prone to reinfection (38). Some women have a mild form of disease and there are many of those who have a colonization of candida without accompanying symptoms and signs. Candida is isolated in 15-20% of asymptomatic women. Pregnancy, antimicrobial therapy, oral contraceptives, diabetes mellitus and immunosuppression are all common predisposing factors for vulvo-vaginal candidiasis (39).

**CLINICAL APPEARANCE** Intensive vulvar pruritus is the principal symptom of vulvar candidiasis. Burning, dysuria, vaginal discharge and superficial dyspareunia may also be present. The symptoms correlate positively with the extent of vulvar erythema. Labia minora may be erythematous, oedematous and excoriated. Small erosions and fissurae are visible in natural folds. Infection can extend to the genitocrural fold, perianal region, into the urethra and even bladder. Usually, the vulva and vagina are affected at the same time. The vagina is erythematous as well, a crudy discharge is present and the plaques of exudate adherent to vaginal walls. There is no mal-odour of the discharge and the pH is lower than 4.

**DIAGNOSIS** Laboratory identification by microscopy and culture.

**TREATMENT** Azole derivatives (miconazole, clotrimazole, fluconazole).

**TINEA CRURIS**

**CAUSATIVE AGENTS** Trichophyton rubrum or Epidermophyton floccosum.

**GENERAL CONSIDERATIONS** Heat and humidity are provoking factors. The infection is most prevalent in women who wear tight occlusive underwear, particularly during warm weather.

**CLINICAL APPEARANCE** Superficial fungal infection of the genitocrural area presented by well circumscribed, small, erythematous, dry, scaly areas that coalesce. Scratching causes lichenification of the skin. The groins are chiefly affected, but the disease may reach the vulva or spread towards the perineum and perianal area either as a continuous rash or as inflamed areas separated by normal skin.

**DIAGNOSIS** Microscopic examination of scrapings from the edge of the eruption suspended in 10% KOH or by culture.

**THERAPY** Imidazol or Clotrimazol cream.

**BACTERIAL INFECTIONS****IMPETIGO**

**CAUSATIVE AGENT** Staphylococcus aureus hemolyticus or streptococci.

**EPIDEMIOLOGY** Autoinoculable, spreads rapidly.

**CLINICAL APPEARANCE** Thin walled vesicles and bullae develop that display reddened edges and crusted surface after the rupture.

**THERAPY** Antibiotics (Neomycin).



Figure 33. Furunculosis on the vulva

**FURUNCULOSIS**

**CAUSATIVE AGENT** Staphylococcus aureus.

**CLINICAL APPEARANCE** Infection of the hair follicle causes vulvar folliculitis. Furunculosis occurs if the infection spreads into the perifollicular tissues to produce a localized cellulitis. Some follicles are palpable as hard, tender, subcutaneous nodules that resolve without suppuration. A furuncle begins as a hard, tender subcutaneous nodule that ruptures through the skin, discharging blood and purulent material

(Figure 33). After expulsion of a core of necrotic tissue, the lesion heals.

**THERAPY** Drainage, antibiotics.

### **ERYSIPELAS**

**CAUSATIVE AGENT** Streptococcus beta-haemolyticus.

**CLINICAL APPEARANCE** A rapidly spreading erythematous lesion of the skin caused by invasion of superficial lymphatics. On the vulva, most often seen after trauma or surgical procedures. Vesicles and bullae may appear accompanied with erythematous streaks leading to the regional lymphnodes. Erythematous vulvitis may be associated with systemic symptoms such as chills, fever and malaise.

**THERAPY** Antibiotics.

### **HYDRADENTIS SUPPURATIVA**

**CAUSATIVE AGENTS** Streptococci or staphylococci.

**CLINICAL APPEARANCE** Refractory infection of the apocrine sweat glands. Multiple, pruritic subcutaneous nodules are seen that eventually develop into abscessus and rupture. The infection tends to involve the skin of the entire vulva, resulting in multiple abscesses and chronic draining sinuses.

**THERAPY** Local cleansing agents (povidone iodide) combined with systemic antibiotics (metronidazole). Anti-androgen therapy was found to be effective as well (40).

### **CHANCROID (ULCUS MOLE)**

**CAUSATIVE AGENT** Haemophilus ducreyi.

**TRANSMISSION** Sexual contact.

**INCUBATION** 3-10 days.

**CLINICAL APPEARANCE** Single, small, painful vesicopustulae appear on the labia, posterior fourchette, perineum or perianally, but may be present in the vagina and cervix too. They rapidly rupture leaving painful, tender ulcers. These ragged, saucer shaped ulcers are circumscribed by an inflammatory wheel. Typically, lesions produce a heavy, foul discharge and 50% of patients have only one ulcer, but cluster of ulcers may develop as well. Sometimes lesion remain in pustular form comprising the so-called Dwarf chancroid (41). In half of patients, painful inguinal adenitis develops which is usually unilateral. Inguinal abscesses (buboes) may become necrotic and drain spontaneously.

Differential diagnosis is from other causes of the genital ulceration/lymphadenopathy syndromes, particularly syphilis,

genital herpes, lymphogranuloma venereum and secondary infected traumatic lesions.

**DIAGNOSIS** Isolation of the causative agent from ulceration or inguinal pus.

**TREATMENT** Erythromycin.

### **GRANULOMA INGUINALE (DONOVANIOSIS)**

**CAUSATIVE AGENT** Calymatobacterium granulomatis.

**TRANSMISSION** Sexual contact.

**INCUBATION** 7-30 days (8-12 weeks).

**CLINICAL APPEARANCE** Chronic ulcerative granulomatous disease that affect vulva, perineum and inguinal regions. Usually no local or systemic symptoms are present. The initial lesion is a red papulae that ulcerates with the development of a soft, red, granular zone with clear, sharp edges. Satellite lesions may unite to form a large lesion. Healing is very slow. Inguinal swelling is common with late formation of abscesses (buboes). Chronic ulceration process may involve the urethra and anal area, leaving scars and stenosis and causing marked discomfort.

**DIFFERENTIAL DIAGNOSIS** Perigenital and perianal donovaniosis lesion may resemble the condylomata lata of secondary syphilis, so serologic test for this disease should always be performed.

**DIAGNOSIS** Histological, by biopsy or curetings of the lesion (presence of the infective agent-Donovan bodies).

**TREATMENT** Tetracyclines or ampicillin.

### **LYMPHOGRANULOMA VENEREUM**

**CAUSATIVE AGENT** Chlamydia trachomatis (aggressive L-serotype).

**TRANSMISSION** Sexual contact.

**INCUBATION** 2-5 days (up to 21 days).

**CLINICAL APPEARANCE** The primary lesion is a small, painless papule or vesico-pustula. It usually appears on the posterior fourchette, although it can be seen on the labia, vagina or cervix. Later, ulcerations develop. Lymphoedema may be present. A few weeks after, lymphadenopathy characteristic for this disease occurs. Inguinal lymphnodes are enlarged, become painful and may suppurate, leaving fistules. Healing is slow, with cicatrisation, rectal strictures, vaginal narrowing and elephantiasis.



**DIFFERENTIAL DIAGNOSIS** Lymphogranuloma venereum must be differentiated from other causes of genital ulcerations or lymphoedema, particularly syphilis.

**DIAGNOSIS** Clinical as well as laboratory (complement fixation).

**THERAPY** Tetracyclines.

## **SYPHILIS**

**CAUSATIVE AGENT** *Treponema pallida* (*Spirochaeta pallida*).

**TRANSMISSION** Sexual contact.

**INCUBATION** 10-90 days, usually 2 weeks.

**GENERAL CONSIDERATIONS** During the last century, the morbidity of syphilis has been declining. Nevertheless, it is still an important infection, particularly since increasing incidence of early syphilis has been documented coinciding with the use of non-penicillin antibiotics treating gonorrhoea. The patient is most infective in the first months of the disease but, if not properly treated, she can transmit the disease for 5 years.

### **CLINICAL APPEARANCE**

1. Primary syphilis. It was long believed that the majority of lesions are localized on the cervix. Recent data, however, suggest that the vulva is much more commonly affected than the cervix (42). The first lesion is a macule, which soon becomes papular. This firm, painless, indurated papule ulcerates leaving a typical lesion called primary chancre (*Figure*



*Figure 34.* Primary syphilis of the vulva

34). It is an indurated, painless oval ulceration with dull red base and raised borders. Vulval lesions may cause marked labial oedema. One week after the primary lesion appears, regional lymph nodes enlarge. They are usually painless, firm and smooth. If not treated, the lesion lasts 3-8 weeks.

2. Secondary syphilis. Two weeks to 6 months (in average 6 weeks) after the primary lesion, general cutaneous eruption of secondary syphilis may appear. Apart from general symptoms such as malaise and fever, skin and mucosal lesions and generalized lymphadenitis are present. Skin rashes are macular, papular, papulo-squamous and pustular. The vulva is affected by skin eruptions including condylomata lata and mucous patches. Condylomata lata appear on the periphery of the vulva and around the anus. They appear as soft, spongy masses with flat

surface and broad base which may coalesce. Erosions which exclude highly infective serum can develop. Mucous patches appear at the same time as maculo-papular skin lesions, which are painless, round and look like greyish-white eroded areas, most often found on the labia minora. With exacerbations and remissions, the secondary syphilis lasts for 9-12 months. After that time clinical signs of infection disappear.

3. Tertiary syphilis. A single chronic ulcer.

**DIFFERENTIAL DIAGNOSIS** It includes invasive cancer, genital herpes, pyogenic lesions, infected trauma site, chancroid, lymphogranuloma venereum, donovaniosis and Behçet's disease.

**DIAGNOSIS** Dark field examination and serology. It should be remembered that serologic tests become reactive 1-4 weeks after the primary chancre.

**TREATMENT** Penicillin or tetracyclines.

## **TUBERCULOSIS**

**CAUSATIVE AGENT** *Mycobacterium tuberculosis*.

**GENERAL CONSIDERATIONS** Although the incidence and mortality of tuberculosis has declined in the developed world, this disease remains one of the most important infectious diseases in the world. The lung is most commonly infected, but other sites, including the genitalia, may be also infected. Vulva tuberculosis may occur as a primary exogenous infection through contact with sputum from a sex partner with pulmonary tuberculosis or with genital secretions when he has renal or epididymal tuberculosis. It may also be due to distal spread from upper genital tract or haematogenous infection from tuberculous foci elsewhere.

**CLINICAL APPEARANCE** In a true primary tuberculosis the initial lesion is an inconspicuous brown-red papule, but this may be missed so that the clinical picture is dominated by inguinal or femoral adenopathy. The primary tuberculous lesion usually heals after a few months, but the enlarged glands may persist and break down. In the chronic stage, fibrosis leads to scarring and vulval lymphoedema. Persistent sinuses may be present. In the other forms of vulva tuberculosis, cutaneous and/or mucosal lesions appear either as nodules that break down to form ulcers with soft and ragged edges or as indurated fungating masses.

**DIFFERENTIAL DIAGNOSIS** Chronic diseases such as lymphogranuloma venereum, donovaniosis, hidradenitis suppurativa and carcinoma.

**DIAGNOSIS** Culture for *Mycobacterium tuberculosis* or histology.

**TREATMENT** General principles of chemotherapy for tuberculosis.

## VIRAL INFECTIONS

### MOLLUSCUM CONTAGIOSUM

**CAUSATIVE AGENT** Molluscum contagiosum virus (MCV) poxvirus, member of Poxviridae family, which includes small pox and vaccinia viruses. Two types of virus have been identified: MCV I and MCV II.

**TRANSMISSION** Close contact with infected person or autoinoculation.

**INCUBATION** 2-6 weeks.

**GENERAL CONSIDERATIONS** Warm, humid environment facilitates infection. MCV infects squamous epithelium only. Over the last years its incidence has increased in sexually active individuals and immunodeficient people. In adults, it is considered a sexually transmitted infection. It has been observed in association with atrophy, malignant disease, chronic use of corticosteroids and immunosuppression such as that of HIV infection (43).

**CLINICAL APPEARANCE** Lesions can be multiple and infect not only the vulva but lower abdomen, pubis and surrounding skin. They never occur on the cervix and vagina. They often appear symmetrically and may be multiple (1-20 single lesions may be found). The typical molluscum lesion is an umbilicated papule. They are usually smooth, round, hemispheric, pearl to skin coloured small lesions. Their size varies, between 2 and 5 mm, rarely exceeding 15 mm. They have a central hole wherefrom a cheesy content can be expressed and typically look like umbilicated papules (Figure 35). Surrounding eczematous reaction or an inflammatory reaction with involvement of the hair follicle and formation of abscess can be seen. Inflammation heralds resolution. In some women, spontaneous resolution happens while in others, lesions can persist for years.

**DIFFERENTIAL DIAGNOSIS** Multiple lesions may be similar to HPV infection and the solitary ones resemble to basocellular cancer. If secondarily infected, they are similar to furuncul.

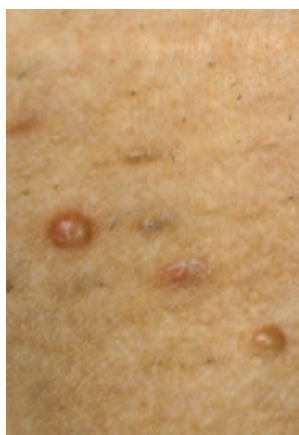


Figure 35. Molluscum contagiosum on the vulva

**DIAGNOSIS** Microscopic examination of biopsy or curettings. Numerous inclusion bodies (molluscum bodies) can be found in the cytoplasm of the cells.

**TREATMENT** It is controversial whether these lesions should be treated. It must be taken into consideration that these lesions are benign and that painful therapeutic procedure may unnecessarily traumatize tissue. Therapy is aimed to prevent further dissemination, relieve symptoms and, in some cases, for aesthetic purposes. Chemical cauterisation (introduction of liquid fenol in the center of the lesion), curettage in local anesthesia or cryotherapy are usually effective.

### HERPES SIMPLEX VIRUS INFECTION

**CAUSATIVE AGENT** Herpes simplex viruses type 1 and 2 (HSV1 and HSV2). The majority of genital lesions is caused by HSV2 type that is slightly different from HSV1, which usually affects lips but may produce genital lesions in 7-37% (44).

**TRANSMISSION** Sexual contact.

**INCUBATION** 3-7 days.

**GENERAL CONSIDERATIONS** HSV infection is a lower genital tract disease, which presents one of the most common sexually transmitted diseases. The infection is very contagious and about 75% of partners of infected individuals will get the disease. About 50% of women with primary genital herpes caused by HSV1 and 80% with primary infection with HSV2 develop recurrences within the year following infection (45). Recurrence of the disease may be provoked by anxiety, stress and may be related to the menstrual cycle or exposure to sun.

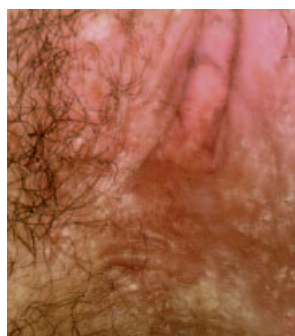


Figure 36. Primary herpes simplex



Figure 37. Eroded vascular eruption

**CLINICAL APPEARANCE** Initially, infection is characterized by prodromal disease, including malaise, chills, fever and enlargement of the inguinal lymph nodes. Lesions can appear on any part of the vulva, but most often affect the labia majora and minora, posterior fourchette, perineum and the anus. Burning and itching may precede skin eruptions by 2-3 days. Small vesicles surrounded by erythematous skin reaction are



Figure 38. Ulcerations in herpes simplex

typical findings, (Figure 36). Vesicular eruptions rapidly erode resulting in shallow ulcers distributed in small patches (Figure 37). These ulcers may be single or multiple, their size is usually 1-2 mm. They are tender, painful but not indurated. On the labia minora the vesicles may coalesce and form large ulcerated areas, with irregular red borders and a pale yellow center

(Figure 38). They may involve most of the vulvar surface. The labia may be oedematous. Dysuria is often present either because of the contact of urine with, inflamed periurethral lesions or due to the development of herpetic urethritis and cystitis. Pain in a severe attack may make the examination difficult. Inguinal and/or femoral lymph nodes can be moderately enlarged by the end of the second week. They are tender but never suppurate.

After reaching their maximum size in 7-10 days, the lesions begin to crust and gradually resolve. After 14-21 days, the healing is completed (46). Fresh crops of vesicles can occur adjacent to such lesions, repeating the cycle of ulceration and healing. This appears in 75% patients and slows down the recovery (44). The infection lasts an average 12 days. About 90% of woman with primary vulvar herpes due to HSV2 and 70% of those infected with HSV1, have a concomitant herpetic infection of the cervix, which is symptomless or manifested by vaginal discharge (44).

Recurrent genital herpes is usually less severe than the first attack. A smaller area of vulvar epithelium is affected. In recurrent disease, ulcers tend to be smaller, fewer in number and confined to one area of the vulva. In many patients, the attack lasts for 2-4 days, exceptionally for 7-10 days. Sometimes, symptoms may be worse than the recidiv disease itself. They manifest locally as itching, burning, hyper- or hypostesia, discomfort and pain. Healing is complete in 1-3 weeks.

**DIFFERENTIAL DIAGNOSIS** Differentiation of herpetic infection from cancer may be difficult. Single, large, atypical lesions may resemble to early invasive carcinoma. Secondary syphilis and Behçet's disease may be considered as well.

**DIAGNOSIS** Diagnosis is established by a smear from the ulceration. Papanicolau smears often demonstrate large multinuclear cells. Isolation of viruses by culture is exact in the first 3 days. When ulceration disappears, negative results do not exclude herpes infection, and the diagnosis can only be made when the next eruption occurs. Serologic test may help.

**TREATMENT** As symptoms and signs of primary herpes are limited by themselves for 2-4 weeks, modification of primary infection requires treatment as soon as possible. Up to now, there is no confirmation that early treatment will prevent latency and recurrences. Previously applied anti-viral agents were potentially toxic and had limited efficacy. Introduction of acyclovir markedly changed treatment and its effective action is maximal provided it is given during the first 2 to 3 days of infection.

## HUMAN PAPILLOMAVIRUS INFECTION (HPV)

**CAUSATIVE AGENT** Human papillomavirus.

**TRANSMISSION** Sexual contact.

**INCUBATION** From one month to 3 and more years.

**GENERAL CONSIDERATIONS** The infection always appears on skin fissurae as the result of close contact with infected persons or their desquamated keratinocytes (47). Autoinoculation is shown by the presence of Koebner phenomenon in which new lesions appear at the site of trauma. In sexually active persons, it is considered a sexually transmitted disease. In approximately 70% of immunocompetent persons infection spontaneously disappears in 2 years (48). However, the virus is never entirely eradicated and it probably remains dormant in the basal keratinocytes. The presence of viruses has been shown in the skin without visible lesions but it is not known yet how frequent this is. Immunodeficiency, pregnancy, contraception and nutrition may increase the risk for the onset of a clinically visible disease (49).

**CLINICAL APPEARANCE** Vulvar HPV infection may be clinically visible and colposcopically detectable (subclinical) or evident by laboratory techniques only (Table 3).

### 1. Clinical HPV infection

When clinical expression occurs, there is an enormous variation in anatomic distribution, disease extent, lesion morphology,

Table 3. Human papillomavirus (HPV) nomenclature

A. Clinical	Evident without magnification or acetic acid
1.	acuminate
2.	papular
3.	papillomatous
B. Subclinical	Better assessed by magnification and/or acetic acid
1.	micropapillary
2.	flat
C. Non-clinical	Evident by laboratory techniques

host immune response and progressive potential. HPV may infect any part of the vulva, but initial changes most often appear on the areas traumatized during sexual intercourse such as the posterior fourchette and labia minora. Most often, condylomas are visible on the labia majora and minora, around the urethra and above the clitoris (Figure 39). They often extend to the lower vagina and sometimes the entire vagina is affected. Posteriorly the infection might extend to the perineum and perianal region, as well as, anal canal. Lesions may also appear in the genitocrural fold and in the pubic region. During the examination, acetic acid is applied and the field is colposcopically examined. It can usually be seen that a considerably greater area is affected than which is visible with the naked eye, and that small lesions are dispersed over a wide area on the labia and around the urethra.



Figure 39. HPV infection – typical condyloma on the vulva



Figure 40. Condylomata acuminata on the vulva

It has been shown that about 10-15% women with vulvar HPV changes have condylomata acuminata on the cervix visible by the naked eye and 50% of patients of those have cytological and colposcopic signs of HPV (50-51). Some authors, however, think that cervical intraepithelial abnormalities in women with vulvar warts are no more common than among controls (52). Clinically visible (exophytic) HPV vulvar lesions may appear as a condylomata acuminata, or papular lesion.

#### a. Condylomata acuminata (venereal warts)

They are benign virus-induced epithelial tumours. The association with HPV 6/11 has been established in 75-95% of cases (53-54). These types of viruses belong to “low-risk HPV” since they are rarely associated with carcinoma. In some cases, condyloma were found to be induced by other “high- or intermediate-risk” HPV. It should be stressed that the morphologic appearance does not necessarily correlate with the HPV type. The clinical implication of a 6/11 HPV infection of the vulva is that it is associated with an increased susceptibility to the acquisition of the HPV oncogenic virus (55). HPV 16 is associated in up to 10-12% of these lesions (53-56).

The morphology is typical and the clinical features are usually sufficient for diagnosis. Condylomata acuminata are most

often visible with the naked eye and usually form multiple papillary or verrucous lesions on vulva. They are frequently multiple. Condylomas are pointed, soft, pink or white, elongated, moist excrescences (Figure 40). Prominently vascularised, they have finger like projections on the surface. Each of these projections is in fact a small condyloma with a central capillary loop which can only be seen colposcopically. Their appearance differs according to the site affected. On the hair-bearing skin they are flesh coloured and somewhat camouflaged. They appear as red hypervascular plaques, white keratotic macules or pigmented papule. On hairless skin they tend to be soft papular and strikingly white. On mucous membranes they are often fleshy, vascular and filiform. Often, they appear along the rim of the labia minora and may be spread to the interlabial sulcus or around the introitus. Typical proliferations which resemble coral may be seen. If more papillae are fused, lesions may get cauliflower shape.

When lesions are dark, clinically it is impossible to tell if they represent pigmented condyloma or pigmented VIN (bowenoid papulosis). Colposcopy and biopsy must be performed in all pigmented lesions to exclude the presence of multifocal VIN 3 or early-invasive disease. Keratinized lesions have a large leukoplakic surface. Even when atypical vessels are not seen, such lesions must be distinguished from cancer, particularly from the rare form of condilomatous cancer (type of planocellular cancer integrated with condyloma).

In patients unsuccessfully treated with podophyllin, the condyloma will often be darker and flatter than usual, with decrease or absence of the spicules typical for the exophytic lesions. In these cases, it is very difficult to distinguish such lesions from VIN. Podophyllin may cause transient histological changes in condylomas which can be seen in biopsy specimen and may present difficulty for histology interpretation (4). Therefore application of podophyllin should be stopped at least 2 weeks before biopsy.



Figure 41. Buschke-Löwenstein tumour of the vulva

Giant condyloma is a rare tumour first described as Buschke-Löwenstein tumour. The disease begins as an apparently straightforward viral wart, but relentlessly enlarges and causes severe destruction to surrounding tissue (57). HPV 6 has been reported in these tumours (58). Clinically, the tumour looks malignant but, in contrast to cancer, it does not metastasize. Histologically, it is benign and resembles condy-

loma acuminatum. It tends to infiltrate underlying tissues and to cause local destruction. These slowly growing tumours may lead to invasive cancer that infiltrate the external genitalia, perineum, anal region and pelvic organs (Figure 41). The nature and reasons for aggressive growth are not known. In the presence of HVP 16 or 18, malignant transformation should be ruled out. Histological examination is essential to differentiate the giant condyloma from squamous cell carcinoma (59).

Vulvar condyloma must be distinguished from other papular conditions, particularly molluscum contagiosum and secondary syphilis lesions, donovanosis, fibroepithelial polyposis and others.

#### b. Papular lesions

These are less common clinical lesions associated with HPV infection of the vulvar skin. These lesions are clinically distinct and may be pigmented or non-pigmented. Less often, they may be associated with depigmentation. The surface of these lesions is above the surrounding epithelium. It is usually smooth, flat and often slightly shiny (Figure 42). Changes are multiple and may be fused. Their diameter is usually 3-7 mm. Biopsy is necessary to identify the nature of these lesions. The papular lesions are often associated in 90% with high-risk HPV 16 DNA (60).



Figure 42. Papular lesions on the vulva

The distinction between warty lesions caused by viruses from VIN and invasive cancer is so important that before any treatment biopsy must be performed for: 1. all lesions that do not have typical appearance and features, 2. all papular lesions, 3. all unusually persistent condyloma, 4. any condyloma resistant to therapy, particularly in young and/or immunosuppressed patients (61).

## 2. Subclinical HPV infections

Subclinical HPV infections may be visualized through the colposcope after the application of 3-5% acetic acid. They are associated with intraepithelial disease (VIN) in 10-20% of cases (62-63). These lesions are distributed around the vaginal introitus, on the perineum and in, perianal areas. They can be asymptomatic, but in many women, their appearance is followed by itching. Sometimes dyspareunia may be present. Their surface is flat or micropapilliferous. Examination by naked eye reveals a normal skin and vaginal smears do not show infection. The natural history of subclinical HPV infection is unknown. It has been estimated that 50% of the lesions spontaneously disappear (7). They must be excluded when vul-

vodinia and vestibulitis are suspected. Colposcopically, subclinical HPV infection can not be distinguished from VIN, making biopsy necessary. Conservative treatment is recommended.

There are a large number of lesions that can be visible only with magnification, i.e. colposcopically. These lesions appear as filamentous lesions or acetowhite epithelium.

#### a. Filamentous lesions (microcondyloma)

Posterior fourchette, labia minora and the introitus are most frequent sites for microcondyloma follows by the external orifice of the urethra, opening of the Bartholin's gland, small openings of the vestibular glands and Skene's glands. Only a few or many lesions may be present, which may be so large that they cover the entire introitus and perianal region, extending to the clitoris, labia majora, surrounding skin and sometimes to the intergluteal fold. Similar changes can be seen on the vagina and cervix.

The lesions are multiple, small, spike-like projections of the vulvar epithelium, which are limited to mucosa (Figure 43).



Figure 43. Filamentous lesions

After the application of acetic acid they become visible as discrete, white spots or white microcondylomas. The individual spike-like projections may occasionally appear to fuse or merge giving the skin granular or velvety appearance. They are largely confined to the posterior fourchette, introitus and the medial aspects of the labia minora. In the hair-bearing skin they can be found associated with follicle. Biopsy confirms the features of HPV infection. Most often, they are caused by infection with HPV 6. It is believed that they present the latent state of HPV infection (63).

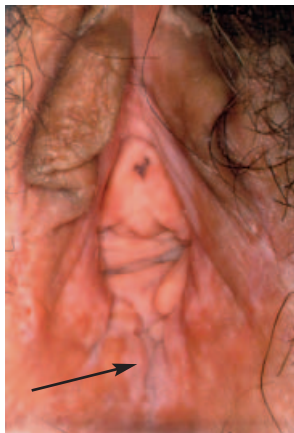


Figure 44. Acidowhite subclinical HPV lesions

#### b. Acetowhite lesions (flat condyloma)

Flat condyloma are usually multifocal. They may cause itching and burning. Colposcopically, they appear as fields of leukoplakia or acetowhite epithelium (Figure 44). On labia minora, fine

punctations similar to those on the cervix and vagina may be seen, because the keratin layer on the surface of this region is minimal. The border is irregular and the surface uneven. Sometimes, large punctations with an increase in intercapillary distance are visible.

**DIFFERENTIAL DIAGNOSIS** The morphology of condylomata acuminata is typical and the clinical features are usually sufficient for diagnosis. The important conditions that should be differentiated from small condylomata are vestibular papillae, which are small excrescences, quite regularly and symmetrically distributed over the vestibular mucosa. The distinction between HPV lesions from VIN and invasive cancer is of great importance, but may be difficult, since these diseases may occur together. Vulvar warts must also be distinguished from other papular conditions such as molluscum contagiosum, condylomata lata of secondary syphilis and donovaniosis.

**TREATMENT** Most human papillomavirus infections respond well to repeated local destruction of lesions until new lesions no longer develop. However, patients with massive disease volumes, refractory lesions and multicentric intraepithelial neoplasia present special problems. Prior to therapy, all patients with external condylomata acuminata should be examined colposcopically. This is important because: 1. superior lighting and resolution of the colposcope helps to ensure that small lesions are not overlooked at the time of therapy, 2. areas of suspect neoplastic changes can be recognized, 3. significant proportion of otherwise unrecognized papillomas (anal, urethral, vaginal, cervical) will be seen (64).

Treatment options for vulvar HPV changes include: 1. scissors excision of isolated lesions, 2. desiccant acids (85% TCA in 70% alcohol, BCA), 3. crude podophyllin extracts (25% podophyllin in benzoin), 4. podophyllotoxin, 5. cytotoxic 5-fluorouracil regimens, 6. alpha or gamma interferon, 7. localized physical destruction (cryotherapy, hot cautery, focal laser ablation), 8. segmental excision and primary closure, 9. extensive electrodiathermy, 10. extended laser ablation.

The perfect destructive modality for cutaneous or mucosal condylomas remains to be discovered. No matter how skilfully applied, no single method is universally successful in eradicating the lesions and preventing recurrence. HPV infections represent regional infections, variably marked by foci of viral expression. Therefore, it is not surprising that the clinical course of most patients often involve a number of recurrences (at either the same or different sites) before host immunity finally control the disease (65). Whatever treatment is applied it is important to destroy all visible disease, because undestroyed papillomas may retard an otherwise competent immune response (64).

## NON-NEOPLASTIC EPITHELIAL VULVAR DISORDERS

### SQUAMOCELLULAR HYPERPLASIA (SCH)

The clitoris, labia majora and the perianal skin are common sites for squamo-cellular hyperplasia (SCH). Microscopically, SCH is identical to Lichen simplex chronicus described on the other parts of the skin. It is believed to be a reaction to chronic pruritus from a variety of stimuli (e.g. recurrent candidiasis, eczema, chemical irritation). SCH is not associated with cellular atypia and is not a premalignant condition. However, it has been found in the skin adjacent to VIN and invasive cancer in 30-74% of cases (53, 66-68).

**CLINICAL APPEARANCE** Attack of itching makes the skin red and swollen. The skin is dry, thickened, slightly scaly and the surface markings are more prominent. Colposcopically, it appears as diffusely delineated, elevated keratinized areas of the skin, without vascular changes (leukoplakia) (Figure 45). On the inner aspect of labia majora, the skin tends to look strikingly white. These lesions usually do not stain blue unless excoriations and fissurae, which are the result of itching, are present.



Figure 45. Squamo-cellular hyperplasia around the labia minora

**TREATMENT** It consists of withdrawal of potential sensitizers and irritants, plenty of bland emollients and topical corticosteroids.

### LICHEN SCLEROSUS

**GENERAL CONSIDERATIONS** Lichen sclerosus (LS) is an inflammatory dermatosis that can affect the skin of any part of the body. Its exact prevalence is uncertain. More

often it affects women: female to male ratio is 6.2:1 (69). Up to 15% of affected patients are children, mainly girls with genital localization of the disease. The underlying cause is unknown, but there seems to be a genetic susceptibility and a link with autoimmune mechanisms. The wart virus and the spirochaete borrelia have been suggested but not substantiated as infective triggers. The Koebner phenomenon is known to occur (Lichen sclerosus occurs in skin already scarred or damaged), so trauma, injury, and sexual abuse have been suggested as possible triggers of symptoms in genetically predisposed people (70). The pathogenesis of this disease is poorly understood. The affected tissue is reversibly atrophic and has normal maturation potential. It was shown that normal skin grafts transplanted to diseased skin are transformed into Lichen sclerosus and that skin grafts taken from the full thickness vulvar Lichen sclerosus transplanted to normal skin, become normal. This mystery remained unexplained until today (50).

The frequency and the significance of the association of Lichen sclerosus and vulvar malignancy has been debated over many decades. There has long been concern over the malignant potential of Lichen sclerosus but there is no definite proof that Lichen sclerosus is a precancerous condition. Lichen sclerosus may exist alone or be complicated by other dystrophic conditions with malignant potential resulting in planocellular carcinoma. Lichen sclerosus was associated with vulvar cancer in 4% cases (67, 71), but there are also reports showing higher incidence ranging from 12 to 47% (68, 72-73).

The histology of LS is distinctive. In the early stage, the epidermis is normal or slightly acanthotic accompanied by hyperkeratosis of different grades. The dermis is initially oedematous and homogenized with mononuclear inflammatory changes located deep in the dermis (lymphohistiocytotic subdermal infiltration). In advanced stages, the epidermis is atrophic while in the stroma, in addition to mild oedema and inflammation, hyalinization occurs.

**CLINICAL PRESENTATION** Although changes presenting Lichen sclerosus occur on any site of the body (trunk, upper and lower limbs), the lesions in women are localized to the vulva and perianal region in 54-60% of cases (15, 70-71). The sites of election at the vulva are the inner aspects of labia majora, labia minora, clitoris and the perineum. The affection of skin is usually symmetrical. Often, these changes involve perianal skin, sometimes resulting in typical appearances described as “figure 8” or “keyhole” (Figure 46). Anal changes can regress or recur as anywhere on the

body, but vulvar lesions seem to be persistent. The most common symptom which differentiates genital and extragenital Lichen sclerosus is pruritus that can be frustrating. Other symptoms are vulvodynia, dysuria, dyspareunia and painful defecation. Anogenital bleeding may be present.

Initially, Lichen sclerosus is asymptomatic and the clinical finding is minimal. (Figure 47). Clitoral oedema with subsequent phimosis may be an early sign of the disease (Figure 48). In the beginning, small, flat, polygonal shape, white to ivory coloured papules appear. These changes are shiny and transparent and may be slightly erythematous (Figure 49). Later, they coalesce making plaques that can be seen together with atrophy. This epidermal atrophy gives the fully developed lesions a parchment-like, wrinkled appearance. Sometimes due to rubbing and scratching the epithelium may become lichenified. Palor of such areas is often striking (Figure 50). When constant pruritus is present, haemorrhagic bullae, purpura or petechias may result from scratching. Sclerosis leads to loss of elasticity and fissuring. Lichen sclerosus may affect not only the skin but mucosa as well. In these cases, mucosa becomes white, often with haemorrhages, telangiectases and bullae. The vagina itself is not involved but stenosis of the orifice occurs, which may ultimately leave only a pinhole meatus which makes intercourse impossible (Figure 51). In advanced cases, the vulvar contours disappear and the labia are lost. The whole field is shiny, waxy and speckled. Adhesions are a further complication, al-



Figure 46. Lichen sclerosus (typical “figure 8”)



Figure 47. Initial Lichen sclerosus



Figure 48. Lichen sclerosus: oedema of the clitoris



Figure 49. Typical skin changes in Lichen sclerosus



Figure 50. Later stage of vulvar Lichen sclerosus



Figure 51. Severe stenosis of the vestibule (pinhole)

though they are infrequent except on the clitoris. In such cases, separation of fused tissue is possible, but readhesions readily occur.

**TREATMENT** Many approaches have been tried over the years in the management of Lichen sclerosus. In the past, most patients were subjected to vulvectomy or even radiotherapy. These aggressive modalities, however, did not appear to be successful and better than conservative therapy. Currently, topical corticosteroids are widely used for vulvar

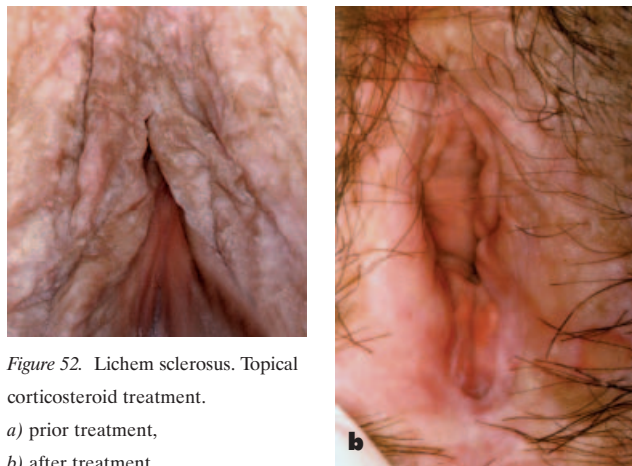


Figure 52. Lichen sclerosus. Topical corticosteroid treatment.

a) prior treatment,  
b) after treatment

Lichen sclerosus (Figure 52a-b). High-grade topical corticosteroid, such as 0.05% clobetasol propionate is used because mild and moderate potency preparations often fail to control disease effectively (74-75). Topical sex steroids are rarely used. Topical testosterone was a therapeutic alternative for a long time. However, virilisation is a common side effect and its superiority over emollients has recently been challenged (76).

**OTHER DERMATOSES**  
**LICHEN PLANUS**

**GENERAL CONSIDERATIONS** Lichen planus occurs on all areas of the skin. Predilectious sites are the flexor surface of the limbs, the perimaloelar and lumbosacral regions and the oral mucosa. In males, in 25% of the cases, the genital region is affected. General conviction was that genital involvement in women was rare. This has led to underestimation of the problem and delay in diagnosis and treatment. The aetiology of Lichen planus is unknown. Current theory suggests that an autoimmune cell-mediated response is responsible for the lesion. Lichen planus eruptions are common among bone marrow transplant patients with graft-versus-host reactions, also suggesting an autoimmune aetiology (77).

**CLINICAL PRESENTATION** Skin changes can be virtually confined to the vulva but more often appear as a part of a widespread eruption. Lesions may be extensive and associated with burning, pain, dyspareunia and postcoital bleeding.

Typically, lesions are tiny, polygonal, glistening papules that frequently show a central umbilication. They are purplish, flat-tapped, sometimes slightly hyperkeratotic (Figure 53). Erosions which may be extensive dominate in clinical presentation.



Figure 53. Typical lesion of Lichen planus on the vulva



Figure 54. Lichen planus: severe vulvar changes

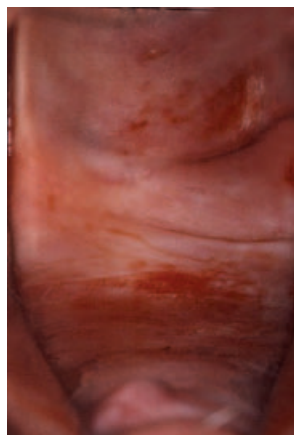


Figure 55. Severe vaginal changes in Lichen planus

They are rimmed by gentle, almost lacy epithelial lesions, which are an important diagnostic aid. In severe cases, scarring and mutilation of the vulva may result (Figure 54).

An uncommon variant of Lichen planus occur on the mucosal aspects of the labia minora and the vagina (Lichen planus erosivus). Mucosal lesions have a characteristic appearance. Sometimes a typical milky white network can be seen on the inner part of the labia minora. Problems appear when only eroded plaques, bulous and atrophic painful areas exist with marked loss of tissue. Vaginal lesions are painful and haemorrhagic (Figure 55). Desquamative or frankly erosive vaginitis occurs, which may lead to adhesions and stenosis making intercourse impossible (78). Perianal changes are also well known to occur in Lichen planus. In some cases, even the cervix may be affected. Examination and biopsy are difficult.

**THERAPY** Therapy is complicated, genital lesions are particularly resistant to therapy, which includes local (topical or intralesional) and sometimes systemic corticosteroids.

**PSORIASIS**  
**GENERAL CONSIDERATIONS** Psoriasis is a chronic relapsing dermatosis that may also affect the scalp, the extensor surfaces of the extre-



mities, the trunk and the vulva. The vulvar skin may be the only body surface affected. Lesions are typically erythematous, resembling fungal infection, but without typical silver scaly crusts that occur on the other parts of the body. In sheltered areas, silvery scaling is lost but the bright erythema and sharp outline remain (Figure 56). Clinical appearance varies from slight erythema to macerated plaques most often localized to labia majora. Lesions on the mons pubis are more scaly. The affection of the genitocrural region is often associated by inverse psoriasis in other flexor surfaces of the skin.



Figure 56. Vulvar psoriasis

**TREATMENT** Local application and intralesional injections of corticosteroids is efficacious.

### INTERTRIGO

**GENERAL CONSIDERATIONS** Intertrigo is an inflammatory reaction which involves the genitocrural folds or the skin under the breast and the abdominal panniculus. It is brought about by warmth, sweating and obesity. The affected area appears either erythematous or white due to maceration. Often, intertrigo has a butterfly shape because it extends from external parts of the labia majora to inner surfaces of the thighs. Lesions are ill-defined, red, moist, sometimes pigmented. An associated superficial bacterial or fungal infection may be present. In these cases, small satellite, scaly lesions can be seen and the main lesion has a macerated, sodden fringe. No other changes of the skin surface are visible.

**TREATMENT** Dealing with predisposing factors, separation of the folds by smooth material such as cotton, mild topical corticosteroids, antiseptics and antibiotics.

### ECZEMA

**GENERAL CONSIDERATIONS** Eczema is a chronic recidivant dermatosis caused by allergic sensibilisation to particular exogenous or endogenous substances which is otherwise harmless for insensible persons. In contrast to dermatitis, which is not the result of sensibilisation and encompasses all changes some agents induce on the skin, eczema is caused by some feature of the skin and not by the external agent itself. This means that some substances cause eczematous lesions only in particular persons. The difference is not anatomic but biologic – the sensitivity of skin. Sensitive individuals develop true allergic reactions to substances which are normally not irritants. These are local antibiotics, anesthetics, antihistaminic, perfumes, local contraceptives and others.

**CLINICAL APPEARANCE** Most often, patients complain of pruritus but this symptom is not specific. If mucous membranes are affected, burning and pain are present. Dyspareunia or tenderness are the result of the exposition of small, colposcopically visible fissures around the introitus to vaginal discharge, sweat urine and seminal fluid. Clinically, it looks like ill-defined erythema of the labia majora and minora, which may extend to the thighs and mons pubis. The vulvar skin usually has a deep red colour (Figure 57). Sometimes vesicles can appear. If the process is long-lasting, the skin may be lichenified, with wrinkling of labia majora and paleness of labia minora. The vaginal mucosa is erythematous and diffusely acetowhite. Secondary infection is common and will produce wet fields of unpleasant odor and acute tenderness.

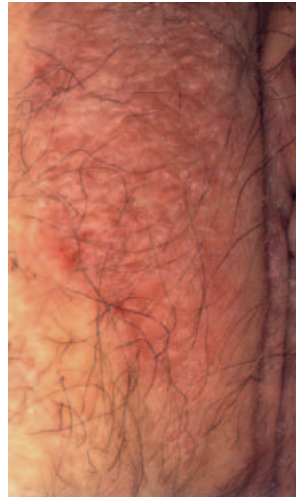


Figure 57. Eczema of the vulva

**TREATMENT** Treatment is withdrawal of any known or suspected causative factor and non-specific local treatment.

### PLASMA CELL VULVITIS (ZON)

**GENERAL CONSIDERATIONS** More than 40 years ago, the presence of glistening red, speckled and haemorrhagic areas on the genital skin of males was described under the name of balanitis circumscripita plasmacellularis. Similar but less obvious conditions in women are rare. It was first described in 1954 (79). Plasma cell vulvitis occurs in the age of 28-89, its aetiology is unknown and it is thought that chronic irritation due to warmth, friction, poor hygiene or persistent infection can contribute to the disease. Maybe this is the type of inflammation of all periorificial places, because cases with oral mucosa and conjunctivae are reported introducing the term circumorifitial plasmacytosis (80). All parts of the vulva may be affected. Although in women the lesions are less prominent than in men, they also manifest as shiny, hyperemic fields almost orange coloured. Often, multiple dark red spots accompanied by pruritus are visible. The epithelium is thin and lichenoid and teleangiectatic changes also appear.

**DIFFERENTIAL DIAGNOSIS** It is difficult because of the similarity with candidais, Lichen planus and Paget's disease.

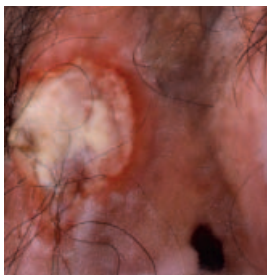
**THERAPY** Therapy is complicated and often unsuccessful. Local corticosteroids achieve different results.

## ULCERATIVE DISORDERS

Apart from already described ulcerative conditions associated with systemic diseases such as Behçet's or Crohn's disease, and certain infections such as genital herpes and syphilis, it is important to mention some other ulcerative vulvar diseases.

### LIPSCHUTZ ULCER

Acute ulcer of the vulva, known as Lipschutz ulcer was first described in 1913 (50). It relates to ulcerations which may be acute (followed by fever and lymphadenopathy) or chronic. The typical lesion is a simple, apthous ulcer, small, painful with a yellow base (*Figure 58*). They usually affect the labia minora and the introitus. Both types of ulcerations lead to scarring. Sometimes they can be visible in the labia majora when they heal leaving minor scars. First type can be seen as a transient problem in adolescent girls without other lesions. It can be present in infective mononucleosis (81).



*Figure 58.* Lipschutz ulcer on the right labium minora

### GENITAL ULCER IN AIDS

Human immunodeficiency virus infection is associated with a wide spectrum of anorectal diseases, of which the most common lesions are anal condylomata and painful ulcers (82). Genital ulcerative disease may be connected with acquiring and transmission of HIV during sexual intercourse. HIV was isolated from genital ulcerations of infected individuals but prevalence and the pathogenesis of this condition has not been investigated much. It is known that in 14% of HIV-positive patients genital ulcerations can be found. This can be a significant clinical problem of the diseased. Recurrence of ulcerations has been documented in 19% of patients with genital lesions, which indicates chronic disease. In 60% of patients with genital ulcerations no infective agents was isolated, in 28% HSV and in 12% unusual and mixed bacterial flora as CMV, CT or gardnerella vaginalis was found (82-83). The clinically most aggressive forms of ulcerations were associated with these infective agents. It is believed that immunosuppression has the important role in the development and exacerbations of these changes.

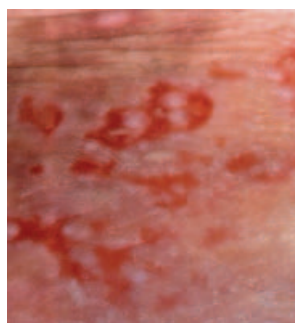
### BULLOUS DERMATOSES

Bulous dermatoses are, regarding aetiology, a heterogenous group of diseases. Some of them may affect the female genital organs and those are: 1. pemphigus vulgaris and pemphigus vegetans, 2. pemphigoid cicatricialis, 3. pemphigoid gestationis, 4. dermatitis herpetiformis – juvenile type, 5. erythema multiforme major (Stevens Johnson, Sy), 6. toxic epidermal necrolysis (Mb Lyell), 7. inherited diseases such as epidermolysis bulosa hereditaria dystrophica or pemphigus familiaris benigna (Hailey-Hailey).

These diseases deserve much attention although they are rare because they are usually erroneously diagnosed. Bulous lesions start with skin tenderness and redness. Although they are significantly different in terms of aetiology and histology, the basic lesion of all these diseases is a bulla, which usually ruptures leaving a more or less eroded surface of dermis exposed to secondary infection. Healing usually results in large scars (scarring).

### PEMPHIGUS VULGARIS

Pemphigus vulgaris is a chronic condition of middle age. Bullae arise from normal skin and are painful, flaccid and eroded in early stages. Cutaneous and mucosal aspects of the anogenital regions are involved and the lesion may affect the vagina and cervix as well. They consist of tight, clear or haemorrhagic bullae that are seen on the normal or erythematous skin. After rupture, painful ulcerations are present, which heal without scarring (*Figure 59*). Chronic and more benign variant occurs in rare cases as heaped-up masses of such lesions – pemphigus vegetans – pemphigus vegetans. Exact diagnosis is established by histology, immunofluorescence, ultrastructural and immunoblotting methods (*Figure 60*).



*Figure 59.* Pemphigus on the vulva



*Figure 60.* Pemphigus vegetans

**THERAPY** Careful nursing and analgesia. Corticosteroid therapy given orally.

Other groups of dermatological disorders are 1. vulvar manifestations of systemic diseases, 2. genetic disorders, 3. disturbances of hair follicles, 4. sweat and sebaceous gland disorders (sebaceous hyperplasia, chromohydrosis, hidradenitis suppurativa).

### VULVAR MANIFESTATIONS OF SYSTEMIC DISEASES

Vulvar manifestations of systemic diseases can be seen in many conditions such as the rare pancreatic tumour-glucagonoma that may present with erythema and bulous lesions, ulcerative colitis presenting with vegetant lesions in the groins similar to pemphigus, sarcoidosis with shallow painless ulcerations, eosinophilic granuloma and others. The most common in this group are Behçet's disease and Crohn's disease.

## BEHÇET'S DISEASE

**GENERAL CONSIDERATIONS** Behçet's disease is a chronic inflammatory multisystemic disorder of unknown aetiology. Originally, it was characterised by a triad of recurrent oral aphthae, genital ulcers and inflammatory eye disease (84). The appearance of genital ulcerations in Behçet's disease may resemble premalignant or malignant vulvar lesions. These lesions, first described by a Turkish dermatologist, Behçet in 1937, may be associated with conditions such as arthritis, thrombophlebitis, skin eruptions (similar to acne), neurological abnormalities and ulcerative colitis (50). Biopsy shows chronic non-specific inflammation with associated vasculitis. Because symptoms manifest themselves over many years the disease can be missed or misdiagnosed easily.

**CLINICAL APPEARANCE** Lesions in oral mucosa appear on the tongue, buccal mucosa, palate and are similar to other aphthous ulcerations. Genital lesions are usually impressive. Predilection site for these lesions are the labia minor. Similar ulcerations can be found in the vaginal mucosa (*Figure 61*). The ulcers are preceded by small vesicles or papules and persist for a variable period of time (weeks or months). The loss of tissue is prominent and causes fenestrations and scarring with progressive loss of vascular tissue. Viral and bacteriological cultures are usually negative, as well as the dark field examination and serological tests for syphilis. The most important is to exclude invasive cancer.

**DIFFERENTIAL DIAGNOSIS** It includes recurrent herpes, recurrent non-treated syphilis and pemphigus.

## CROHN'S DISEASE

Skin lesions and mucosal lesions in the oral cavity may precede intestinal disease by up to several years (85). Anogenital manifestations of Crohn's disease are well recognized. In 25-30% cases they may affect the vulva or perineum (86-87). The lesion can be a direct continuation of bowel involvement. If there is normal skin between the lesions, particularly if they are clearly separated from the anogenital region, they are referred to as metastasis. Histology shows necrotizing epithelial granulomas.

The usual appearance of the lesions are ulcerations which may affect the groins and the abdominal wall. Lesions are usually linear, include loss of tissue and usually have a clear base. They look like "knife cuts" in the skin. Fistulae, abscesses, oedema of the perianal folds and the vulva may be present. Vulvar oedema may be the only dermatologic manifes-

tation of Crohn's disease and it is typically unilateral. Vulvar and perianal lesions may cause dyspareunia.

## NEOPLASTIC EPITHELIAL VULVAR DISORDERS

**VULVAR INTRAEPITHELIAL NEOPLASIA (VIN)** The concept of vulvar intraepithelial neoplasia has been accepted for more than a decade. Recent knowledge about the natural history of VIN has broadened providing more information about epidemiology, pathology and clinical management of these diseases. One of the most important points was the introduction of revised classification of vulvar diseases, which suggests the term VIN as the replacement for many confusing names that have been used before, such as atypical hyperplastic dystrophia, Bowen diseases of the vulva, Bowenoid atypia, Bowenoid papulosis, planocellular carcinoma in situ, erythroplasia ouerat, leukoplakia and mild to severe dysplasia (86). Similarity with CIN terminology is the division of VIN in VIN 1, VIN 2 and VIN 3. The characteristics of VIN are similar to those of CIN in that it consists of atypical cells limited to epithelium.

The exact prevalence of VIN is difficult to estimate, but according to some reports, the prevalence of VIN 1-2 is 0.2% and that of VIN 3 is 0.4% in women over 35 years (87). During the last decade, there has been a substantial increase in the prevalence of vulvar intraepithelial neoplasia (88). The increase is particularly significant in young women (89-90). The annual incidence of VIN 3 has been shown to be 2.1/100,000 women (88). Most often, VIN occurs in women in their reproductive period. 49-50% of patients are younger than 40 (88, 91). The mean age in which the disease is detected is from 35 to 40 (91). Risk factors for this disease are early first intercourse, more partners, smoking, immunosuppression and HPV infection (92). There is strong association (23-60%) between VIN and other sexually transmitted diseases (93). Patients with VIN have a higher risk of intraepithelial neoplasia on other parts of the lower genital organs, and 7.9-30% of them have concomitant CIN or VAIN (4, 90). Diagnosis of VIN requires detailed examination of the cervix and vagina.

In the last years, special interest has developed concerning the role of HPV infection in the onset of VIN. The presence of HPV changes in a high proportion of VIN is highly suggestive of such a role. The viral integration into the cell genome and development of aneuploidy seem to be the main factor in the development of invasive carcinoma (94). In women with HPV findings in a PAP smear, 44% have vulvar changes that can be designed as atypical. Twenty to fifty percent of VIN lesions are associated with vulvar condyloma (4). HPV is detected in more than 80% of women with VIN 3 and mainly it is HPV 16 (95). These findings suggest similar biological behavior of VIN and CIN. However, it is well



*Figure 61.* Behçet's disease localized in the vagina

known that these tissues are embryologically different. The probability that VIN 3 will progress to invasive cancer is much lower than that of CIN (3-17%), regardless of the associated HPV type. In contrast to the cervix, active metaplastic processes, which make cells susceptible to carcinogenic factors, do not take place on the vulva (15, 96-97). Nevertheless a majority of practitioners consider VIN a pre-malignant lesion. It is well known that untreated VIN can progress to invasive cancer, but it is also known that spontaneous regression can occur, more often than in CIN (98).

**CLINICAL APPEARANCE** Approximately 50% of patients with VIN complain of pruritus, irritation or visible vulvar lesions, which are, in half of the cases, larger than 2.5 cm. In others, the lesions are diagnosed by chance, during the examination (91, 94). A small number of women will notice some type of vulvar lesion. VIN is usually present on the inferior parts of the labia majora and minora, posterior fourchette, perineum, periclitoral area and around the anus. The perianal area and the anal canal are involved in 14-35% cases, particularly those in whom the posterior part of the vulva is most severely affected (99). Also, there may be associated changes, such as Lichen sclerosus and squamocellular hyperplasia, within the skin surrounding VIN 3 in 20-40% of the cases. (67, 89, 100).

Clinical features of VIN 1 and 2 are not well documented and a majority of reports refer to VIN 3. The clinical appearance of VIN is variable, significant variations present in colour, surface and topography (Figures 62-63). Lesions are solitary or, in 70% of the cases, multiple. Recently, it was reported that in women younger than 45 years the lesions are multifocal in 63.2% of the cases, while in women older than 45 years this percentage accounts only 31.8% (90) They are characteristically papular, raised above the level of surrounding skin, often with sharp borders and a keratotic, roughened surface. Lesions can be dry or wet and often resemble to condylomata acuminata, which are usually associated with VIN (101). Discolouration is usual and lesions may be variegated with areas of brown, red, blue and white colouring. White lesions reflect epithelial thickening and hyperkeratosis, red lesions

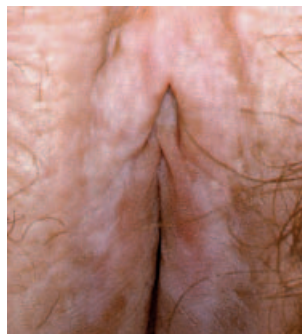


Figure 62. VIN 1



Figure 63. VIN 2

hypervascularity and parakeratosis and grey or brown lesions are due to melanocyte overactivity and pigment incontinence. More than half of these lesions show superficial parakeratosis, and become stained when toluidin blue test is applied (87). Vascular aberrations typical for the cervix, however, are less remarkable, except if VIN is present on the labia minora, in which cases a mosaic pattern and punctations can be evident.

*Park et al.* (102) described two dominant histological patterns: a Bowenoid (wart) VIN characterised by dyscariotic acanthotic cells showing partial but disordered maturation, and a basaloid VIN characterized by an epithelium composed completely of atypical immature parabasal cells. The Bowenoid type was associated with a high frequency of HPV 16 and lower incidence of invasive vulvar cancer.

Clinically, two distinct forms of VIN can be seen. The first develops in young women and is multifocal and multicentric, and the second appears in older women and is usually unicentric. The first type that appears usually before the menopause is more common than the unifocal type that is present after the menopause. Occasionally, these two types of VIN can be found together (94)

The differences between these two types of VIN have been described a long time ago. *Bowen* described these diseases in 1912 when, after the follow-up of patients during 12 to 16 years, he noticed that neither curettage nor cauterization eradicate multifocal lesions, and that these lesions did not show the progression to full thickness of the epithelium. In contrast to this, isolated lesions in older patients did show progression (86). So, historically the first type of VIN was described as Bowenoid papulosis and the second was as Bowen's disease.

Bowenoid type of VIN 3 (Bowenoid papulosis) very seldomly progresses to invasive cancer. The lesions are typically multiple, discoid, usually pigmented and can affect the whole external genital organs, including the perianal skin (Figure 64). Some of the pigmented forms of Bowenoid VIN have specific clinical appearance described as flat grey-brown lesions, hyperpigmented raised lesions, papillary or verrucous lesions (101, 103-105)

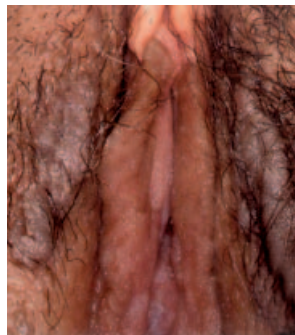


Figure 64. VIN 3 (Bowenoid papulosis)

These lesions primarily occur in young women and it is long believed that they do not present any risk for malignancy.

It is noticed that spontaneous resolution often appears within 6-12 months (105). It is also reported that spontaneous regres-

sion can take place after biopsy (106). However, some authors have described more advanced nuclear changes than the ones found in the original descriptions including enlarged nuclei, multinucleation and aneuploidy. Therefore it is possible that these lesions are more significant than first described and their general clinical appearance as well as association with typical VIN points out that Bowenoid papulosis should not be excluded from the spectrum of precancerous vulvar lesions (107). CIN can be associated with these type of vulvar changes.

Bowenoid type of VIN 3 (Bowen's disease) is usually the disease of women older than 50 (Figure 65). During the last decade, there has been an increasing incidence of this type of VIN in young patients. The significance of this clinical classification is that they probably point out that the two types are associated with different HPV types and have different malignant potential.

**VIN IN PILOSEBACEAL UNITS** The vulva is covered by hair-bearing and non-hair-bearing skin. This is necessary to know when the possibility and size of affection of pilosebaceous units is concerned. VIN can be extended to pilosebaceous units. When it is extended to hair follicles and/or sebaceous glands, it is in all its aspects similar to CIN extending to endocervical glands. When VIN 3 is present in pilosebaceous units it reaches the depth of 2-2.8 mm in both hair-bearing and non-hair-bearing skin (86). Recognition and diagnostics of VIN in pilosebaceous units is important because its clinical significance is not neglectable.

Clinical evaluation of all VIN lesions, particularly high-grade ones, should be done very carefully, because an underlying early invasive squamous cancer, according to different reports, appears to be present from 16 to 22% of patients (97, 108, 109, 110)

**DIFFERENTIAL DIAGNOSIS** Since the clinical appearance of VIN varies considerably, lesions can mimic squamocellular hyperplasia, Lichen sclerosus, psoriasis, Paget's disease or acute reactive vulvitis. Diagnosis can be achieved by biopsy only and the multicentric nature of the lesions requires multiple biopsies.

**TREATMENT** There is little consensus regarding the optimal method of management. The aim of treatment is to con-

trol symptoms and/or progression without altering appearance or function unnecessarily. In addition, it is important that management should be safe as this premalignant condition has an uncertain potential for progression to invasive disease.

It may be possible to manage VIN 1 and VIN 2 in a more conservative manner because their risk of progression appears to be low. It has recently been reported that one third of VIN 1/2 lesions persist or recur after the treatment (90). The risk of progression of VIN 3 may well be higher than previously suspected and these patients merit careful and long-term follow-up. Spontaneous regression of VIN 3 was documented, but this is more likely to happen in very young women (mean age 19.5 years) who have multiple and pigmented lesions (98). Clinical evidence shows that in 3-17% of patients will VIN 3 progress to invasive squamocellular cancer of the vulva (96-97). In the absence of definitive information about the natural history of VIN and its risk of progression, treatment should be undertaken not only to control the symptoms, but also to prevent a potential malignant transformation.

A large number of modalities have been advocated for treatment of VIN: 1. conservative management, 2. medical therapy (5-FU), 3. laser treatment, 4. wide local excision using a knife or laser, 5. skinning vulvectomy and skin grafting, 6. simple vulvectomy. In general, patients treated with excisional techniques had significantly lower recurrence rate compared to those who underwent ablative procedures (91, 97).

### MELANOMA IN SITU

Vulvar skin consists of only 1% of total skin surface, yet 5% of all melanomas in women arise in this region. They are present as superficially spreading lesions that occupy an extensive area. They can arise anywhere on the vulva but are most likely to occur in the non-hair-bearing skin, especially around the labia minora and the clitoris, urethral matus and/or the vagina. The majority of melanomas, 60-70%, have superficial growth (melanoma in situ) that for many years precede the invasive phase of the vertical growth (see malignant melanoma at invasive neoplasia). Treatment is surgical.

### PAGET'S DISEASE

First description of the disease was published in 1874 by Sir James Paget (111). At that time, it was believed that this disease, which occurred on the nipple and mammary areola, is exclusively associated with breast cancer. Later, it was noticed that similar changes may be associated with vulvar cancer. Paget's disease of the vulva first described *Dubreullih* in 1901, as the presence of secretory, glandular cells of adenocarcinoma in the vulvar epidermis and the skin appendages (112). Until 1955, in world literature only 23 cases of vulvar lesions corresponding to Paget's disease were reported (113). Later it was shown that Paget's disease of the vulva is more frequent



Figure 65. VIN 3 (Morbus Bowenii)

and that it includes multiple localizations. For less than 10 years, 98 new cases of vulvar Paget's disease were reported, 23 of which were associated with or preceded invasive cancer (114).

Paget's disease of the vulva is rare and accounts for less than 5% of all vulvar malignancies (115). It occurs in ages of 38-86 (average 63 years). In up to 50% of cases, Paget's disease of the vulva appears to be associated with vulvar adnexal carcinoma or other local tumours such as carcinoma of the Bartholin's gland or distant tumours like breast urologic or gastrointestinal cancer (115-116). Paget's disease of the vulva is rarely associated with an underlying vulvar adenocarcinoma (4%) or invasive Paget's disease (12%), but there is a high recurrence rate (117-118).

Histology is quite typical with its content of large, clear "Paget cells" or as that lack intercellular bridges and have pale, vacuolated cytoplasm within the squamous epithelium (119). The clarity of microscopic appearance of the cells is due to their mucin production. They are situated in line or in nests near the basal cell layer (120). As epithelium matures, the cells can be progressively found in the upper layers and approaching the surface, detaching keratinized squamous epithelium.

Pruritus, soreness and a burning sensation are the most frequent complaints and may be present from several months to 10 years (118). They often arise on the labia majora, but may affect the perineum and the perianal region. Sometimes, they can extend to the inguinal folds, mons pubis, labia minora, vestibule and the vagina (121). Even cases with extension of Paget's disease to the cervix have been reported (122).

Paget's disease appears as slowly spreading ulcerative eczematoid lesions of the vulvar skin. Characteristic clinical findings are the so called "weeping" Paget's disease that affect moist parts of the vulva. In these fields, areas of hyperkeratotic tissue interspread with rivulets of raw red tissue exist (15). Multiple, erythematous, eczematous changes can be seen, well separated from the surrounding skin (*Figure 66*). They are scaly and resemble a geographical map. Sometimes, the patches are hyperkeratotic and white, occasionally however, they are papillary. On hair-bearing areas this is usually treated as local infection which leads to the delay of proper diagnostics.

The treatment is surgical – wide local excision. During the treatment, careful examination of all vulvar localiza-



*Figure 66.* Vulvar Paget's disease

tions must be performed, because the disease is often multifocal, and treatment basically is wide excision (115). This wide local excision should be controlled by ex-tempore biopsy of the resection margins. Recurrences are treated by further excision. This is necessary because Paget's disease spreads beneath the clinically visible margins.

### INVASIVE VULVAR CANCER

Malignant diseases of the vulva comprise 4% (3-8%) of all primary malignancies in female genital system (123). The most frequent is planocellular carcinoma that is diagnosed in 90% of women, malignant melanoma 5%, 4% of the tumours are described as unidentified and the rest are sarcomas, basocellular carcinomas and primary carcinoma of Bartholin's gland. Ten percent of the primary carcinomas have been shown to have metastatic disease (124).

### PLANOCELLULAR CARCINOMA OF THE VULVA (SQUAMOUS CELL CARCINOMA)

Planocellular vulvar cancer has an incidence of 1.5 per 100,000 women (125). An increasing incidence of this disease has been reported, particularly in young women (88, 126-127). It can be detected in any age, from 14 to 95 years, but the average age for this disease is 60 years (128). It is characteristic that the incidence of planocellular carcinoma increases with age and in women older than 75 the incidence accounts for 20/100,000 (129).

The aetiology in most cases remains unknown. The tumour is often associated with advanced age, nuliparity, poverty, unmarried state, earlier than average menopause, premature atherosclerosis and immune deficiency (130). At young age at first sexual intercourse, multiple sexual partners, a low socio-cultural level, previous infection by human papillomavirus and smoking have also been identified as risk factors (131). There is no data to suggest that invasive vulvar cancer is hormone dependant.

In the past, two types of squamocellular cancer of the vulva have been delineated: HPV-positive and HPV-negative. Recent studies have emphasized clinicopathological differences between these cancers (132-135). HPV-positive carcinomas account for 22-80% of cases (53, 132, 134-136) and known to arise within the field of VIN and occur in women whose mean age is 3-22 years. They are younger than those with HPV-negative carcinomas. Most exclusively it is associated with HPV 16 (53, 134, 137). As these infections have an increasing trend, particularly in the young population, it may be expected that in the future this type of invasive vulvar cancer will be more frequently diagnosed in young women (138).

While the possible aetiological role of HPV infection in the genesis of vulvar cancer has been partly elucidated, the gene-

sis of HPV-negative vulvar cancer remains obscure (139). The traditional view is that it is induced by chronic irritation. Indeed, this type of cancer is arising within an area of Lichen sclerosus or squamocellular hyperplasia. Lichen sclerosus was found in 60% and squamocellular hyperplasia in 80% of HPV-negative vulvar cancers (137). *Scurry* (140) recently proposed “The itch-scratch-Lichen sclerosus hypothesis” as the possible explanation of the pathogenesis of vulvar cancer. The reported incidence of histologically confirmed Lichen sclerosus in vulvar tissue removed from carcinoma varies from low levels of 7-9% to, using subtle criteria, high levels of 96-100% with the mean about 50% (66,141,142). The question remains whether Lichen sclerosus has the role in the pathogenesis of vulvar squamocellular carcinoma, since itching and scratching alone do not explain close association of vulvar cancer and Lichen sclerosus, nor the absence of other itching conditions such as eczema or psoriasis (140).

**CLINICAL APPEARANCE** Diagnosis of clinically visible invasive cancer usually does not require colposcopic examination. The value of colposcopy in these lesions is most evident in early stages of the disease when patients are treated with local preparations for other problems because the cancer is not recognized. At that time, colposcopy can distinguish the fields different from surrounding skin and with biopsy the invasive cancer can be identified. Colposcopy also can help in evaluating the extent of the involvement of the vulva and in delineating the margins of the surgical specimen to be removed.

Invasive vulvar cancer may be asymptomatic. If symptoms and signs are present, they include pruritus, pain, bleeding and/or the presence of a palpable lesion. The majority of the tumours, approximately 70%, arise on the labia, more often labia majora. In 40% of the cases, it can appear in the labia minora and in 9-15% the clitoris and the perineum are affected (143). The lesions are multifocal in up to 30% of the cases and 5 separated lesions have been reported. In 10% of the patients, the tumour is too large to define the site of origin. More than half of the tumours (57.2-62%) are ulcerated, about 1/3 (27-40%) papillary and in the remaining cases (10%) they are presented as flat lesions. In 10-20% of the patients, the disease is multicentric and often a symmetric, bilateral “kissing” vulvar tumour can be seen (*Figure 67*).



*Figure 67.* VIN 3 and early invasive cancer of the vulva

Clinical features of early invasive cancer are the same as of VIN 3, except that early lesions may be more elevated from



*Figure 68.* Microinvasive cancer of the vulva



*Figure 69.* Small invasive cancer of the vulva



*Figure 70.* Frankly invasive cancer of the vulva

the surface, rough and pigmented (*Figure 68*). Diagnosis of early invasion can not be made clinically because of the similarity with VIN. Indeed, 7-22% incidence of unexpected early invasion was reported in high-grade VIN (97, 108-109, 144). It can only be suspected that early invasion exists. For exact diagnosis biopsy is necessary. It should be excisional with the margins of the surrounding skin of normal appearance of 1-2 cm. Wide excision is not the problem when the lesions are isolated, solitary and well-defined. In extended, multicentric lesions, multiple biopsies are necessary. Also, elective simple vulvectomy or skinning vulvectomy may be useful in diagnosing the disease.

Lesions of frankly invasive cancer are usually raised, they can be red or white and typically ulcerated (*Figure 69*). Usual colposcopic criteria for invasion include 1. necrotic fields of yellow appearance, 2. abnormal vessels running in corkscrew fashion, parallel to the overlying epithelial surface along with irregular dilatation producing a bleeding effect (*Figure 70*).

It is also important to realize that vulvar carcinoma can be associated with changes to the skin surrounding the carcinoma. Pathologic alterations in the adjacent epithelium such as squamocellular hyperplasia, Lichen sclerosus and VIN are present in 60% of vulvar carcinomas (145). According to more recent reports, only 5% of the patients treated for squamocellular cancer did not have synchronous epithelial changes (68).

The cancer is spread directly to the surrounding tissue, by lymphatics to the inguinal, femoral and pelvic lymphnodes, and rarely by blood to bones. In 30% of the patients inguinal metas-

tases are present at the time of diagnosis (146).

### Verrucous carcinoma

A special form of invasive vulvar cancer is the verrucous carcinoma. This type of cancer is rare and it is very difficult to distinguish it from condyloma. These tumours usually appear in older age. Most patients are in post-menopause, in 80-90 years, the tumour, however, may occur in young women, the youngest one reported was 21 (124). Fifty percent of the cases had biopsy proven condylomas up to 10 years before the diagnosis of vulvar cancer. Lesions can spread very fast, growing to a considerable size, and causing the patient difficulty with mobility. The appearance of the tumour is typically condylomatous or papillary. It may have the shape of fungus or may look like an ulcerated mass of cauliflower shape. It can be grey, pink, yellow, white or pigmented as the surrounding skin. The most typical site of occurrence is the labia majora (Figure 71). Occasionally, it affects the entire vulva.



Figure 71. Verrucous cancer

Natural history of the tumour growth shows local invasion and tendency to recur. If primary excision is incomplete (sometimes it is difficult to ensure complete excision), the recurrence is inevitable in 1/3 of the cases. Tumour relentlessly invades adjacent structures, even bones and perineural infiltration has also been seen. Lymphatic spread can happen but it is exceptional as the distant metastases are.

### MALIGNANT MELANOMA

Malignant melanoma (MM) of the vulva occurs more often than should be expected in terms of the proportion of total skin surface accounted for by the vulva and represents 4-9% of all vulvar cancers (147). The incidence of this disease is estimated to be 0.19 per 100,000 women (148). Malignant melanoma is not seen in girls before puberty, but afterwards its incidence gradually increases and reaches a peak in the 6-7 decade. Mean age for malignant melanoma is between 54 and 60 years. History is usually short, a few weeks to 8 months, although symptoms may be present for over a year before. Burning or itching may be present. Initially a small lump or bleeding mass can be seen. Many women report that they have noticed changes in previously long-standing vulvar nevi. Sites can be different but usually changes are localized centrally, in the labia minora and the clitoris. FIGO clinical staging recommended for vulvar cancer applies to malignant melanoma as well. In most series, 60-70% of the malignant melanomas have superficial spread, while the remaining belong to the nodular type (149). One part of these superficial melanomas will come to the phase of vertical growth and evolve to nodular form.

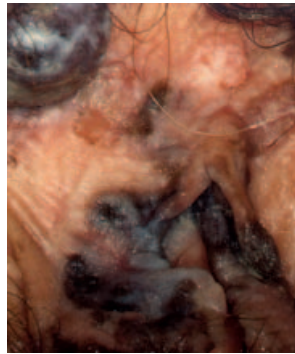


Figure 72. Malignant melanoma

Nodular malignant melanoma has vertical shape of growth only. It does not have any previous stages of radial growth and has very invasive properties in early stages. Histologically, the lesion consists of discrete nodules or masses of invasive malignant melanocytes which spreads both downwards to the dermis and upwards to the epidermis.

Melanoma can be presented by superficially spread lesions, which affect a large area. They can appear in any part of the vulva but most often in the non-hair-bearing areas, particularly around the labia minora and the clitoris (Figure 72). They can also be found in and around the external urethral orifice and/or vaginal introitus.

Melanoma may be flat, elevated (nodular) or polypoid and is often ulcerated. Characteristically, it has brown to bluish-black colour but a small percentage is amelanotic and microscopically resembles planocellular carcinoma. These non-pigmented forms of malignant melanoma appear in 10% of the cases (150). Usually, malignant melanoma is surrounded by a reddish flare which indicates the presence of a cellular immune reaction to neoplasm. Satellite skin metastases can be present.

Prognosis of malignant melanoma depends of the depth of invasion measured by the *Clark* scale (151) and thickness according to *Breslow* scale (152). These two parameters are the most significant prognostic factors for local recurrence and regional lymphatic spread.

Radical local excision is the recommended treatment and in patients that have more than superficially invasive melanoma, inguinal node dissection should be performed. Radical surgical approach does not improve long-term prognosis (153)

### BASOCELLULAR CARCINOMA

Basocellular carcinoma is rare and makes up only 2-10% of vulvar cancers. It occurs in an older age group (between 58-73 years) with no identifiable predisposing risk factors and does not show evidence of HPV infection (154). It has been suggested that chronic infection, trauma, vaginal discharge or radiotherapy and, in the past, arsenic preparations may increase the risk for development of basocellular cancer. Immunocompromised patients have increased risk not only for the development of this cancer but also for a second malignancy, which is found in 20% of elderly patients.

There is no evidence that a preinvasive stage of basocellular cancer exists. It can be associated with Lichen sclerosis. His-



tologically, it originates from the epidermis, pilosebaceous units or sweat glands and consists of small, round oval or slightly elongated cells with deep basophile nuclei and meager cytoplasm. Clinically, it is presented by pruritus, serous or blood stained secretion and bleeding. Symptoms may be present for 3 weeks to 3 years before the exact diagnosis is established. There is often a delay in diagnosing the diseases due to lack of symptoms. Diagnosis requires biopsy.

Most of these lesions are limited to the labia majora, although they can appear around the clitoris, mons pubis, urethra and the posterior fourchette. Size varies between 1 and 7 cm and, rarely, their diameter can reach 10 cm. They may form nodules with or without ulceration, exophytic lesions or fields of excoriation. Basocellular carcinoma presents as erythematous, polypoid, papillomatous, cystic or plaque-like lesion. When containing melanin, and this happens in 1/3 of the cases, they resemble clinically to malignant melanoma. Variable appearance of basocellular carcinoma often makes diagnostic difficulties, particularly if inguinal lymph nodes are enlarged due to secondary infection or local ulceration.

This cancer is locally aggressive and has a very low propensity for metastatic spread (155). The treatment of choice is wide local excision. Lymphadenectomy is indicated only in the presence of enlarged or suspicious inguinal lymph nodes. Because of a substantial risk of local recurrence and high frequency of other primary cancers, close long-term follow-up is essential (156).

#### **OTHER MALIGNANT TUMOURS OF THE VULVA**

Carcinoma of the Bartholin's gland accounts for 0.1-7.25% (in average 2.25%) vulvar malignancies. The mean age at presentation varies between 50 and 65 years but it was reported in as young as 14 year-old girls and even in pregnancy (157). It can usually be seen as firm mass, deep in the posterior part of the labium major often producing perineal pain. It can extend superiorly to the vagina, posteriorly into the rectal sphincter and the ishiorectal fossa and anteriorly along the labia majora. The size may be between 1-6 cm. The tumours are usually solid and grey-white on section. Skin over the tumour does not often ulcerate but spontaneous drainage can happen due to associated abscess. Overlying and adjacent epithelium can display the features of Paget's disease. There is considerable delay (sometimes several years) between the onset of symptoms and the correct diagnosis. The delay is due to the fact that in 25% of the cases the presenting problem is the abscess of the gland and only when the lesion does not respond to usual antibiotic treatment or an incision, the possibility of an underlying serious condition is considered. Therefore, it is very important to thoroughly investigate the cause of the Bartholin's gland abscess in older women or persistent infection in

younger the both histologically and cytologically. Histology shows planocellular, adeno- or adenoid cystic carcinoma.

Non-epithelial malignant tumours of the vulva comprise of a large group of malignant neoplasms originating from mesenchymal tissue (sarcoma). They are not frequent, all appear as vulvar enlargement and although asymptomatic specific diagnosis is readily made due to the presence of a large vulvar mass. Sometimes, they can be pedunculated due to gravitation effects, ulcerated or secondary infected. Sarcoma can originate from any mesenchymal tissue: smooth muscle (leiomyosarcoma), striated muscle (rhabdomyosarcoma), fibrous tissue (fibrosarcoma), fat (liposarcoma), vascular (haemangiopericytoma, angiosarcoma, Kaposi's sarcoma) lymphatic (lymphangion) or neural tissue (neurolipoma, neurofibroma, neurofibrosarcoma – Schwannoma). In addition to sarcomas, germinative cell tumours such as endodermal sinus tumour or teratoma can appear.

Kaposi's sarcoma (KS) deserves to be addressed separately because more cases have been seen since HIV infection became wide spread. Before the increase of incidence of AIDS, Kaposi's sarcoma was a rare disease. Now, it is the most frequently seen malignancy in AIDS. Recently, type 8 of herpes simplex virus (HSV 8) has been implicated as the sexually transmissible agent that causes Kaposi's sarcoma (158). In women, Kaposi's sarcoma is less frequently seen than in men, but in those where it is diagnosed the source of HIV infection is the contact with a bisexual partner. It may occur at any stage of HIV, but in over 80% of the cases it affects patients who have less than 500/mm<sup>3</sup> CD4 lymphocytes. It appears on the areas of old trauma or previously existing dermatosis. In more than 20% of the cases, the lesions affect the oral mucosa and the hard palate, often involving ocular structures. Nowadays, when Kaposi's sarcoma becomes more frequent in women, this disease is also seen to affect the vulva (159).

It is a multifocal vascular tumour, usually seen as bruise-like erythematous to violaceous macule or violaceous papule similar to bruise. The lesion gradually enlarges and gets the appearance of plaque or nodule. These lesions have the tendency to ulcerate and become hyperkeratotic (tappero). Chronic ulcerative lesions, chronic traumatic lesions and oedema are the subject of secondary bacterial infection, most often caused by pseudomonas aeruginosa, staphylococcus aureus or anaerobes. Lesions may develop at the site of trauma or pre-existing dermatosis.

#### **METASTATIC DISEASES OF THE VULVA**

Vulva is the site of metastases for tumours of other gynaecological organs, but also of the urethra, kidney, breast, rectum and the lungs. Besides these predominantly adenocarcinomas, choriocarcinoma, melanoma and Burkitt lymphoma may

metastasize to the vulva. Often, both the metastatic lesion and the primary tumour are diagnosed at the same time and this happens in 27% of the cases (150)

Vulvar metastases are usually situated in the dermis or subcutaneous fat tissue of the labia majora and around the clitoris. They are consisted of homogenous, greyish-red tissue and, although usually one tumour node appears, it is not unusual to find several nodules (Figure 73). Expansive growth, multiple lesions and the absence of intraepithelial neoplastic changes, are in favour of metastatic tumour. In rare instances, they may mimic cellulitis with red and painful skin, and this is the so-called inflammatory cancer. The presence of vulvar metastases is associated with unfavourable prognosis and indicates disseminated malignancy.



Figure 73. Vulvar metastatic disease

Trophoblastic tumours such as choriocarcinoma are not frequent, but they have a tendency to give metastases to the vulva and vagina. These metastases usually are noticed as livid nodules, which have a smooth surface and arise from the vaginal mucosa or vulvar skin. Malignant lymphomas and leukemia have been reported to give vulvar manifestations. They are soft, elastic and prone to bleeding. Individual blood vessels cannot be clearly seen. Although the appearance of the tumour is not characteristic, in patients known to have trophoblastic disease, any such vulvar lesion must raise suspicion to metastasis. Biopsy can be very dangerous because of possible heavy bleeding. Adequate and successful chemotherapy can result in complete disappearance of the lesions.

### COLPOSCOPY OF THE PERINEUM AND THE ANAL CANAL

Anal colposcopic examination (anoscopy) is very important in defining the extent and features of lesions of the anus, anal canal and the perianal area. Colposcopy of the vulva seems to be an invaluable aid in assessing the nature and the extent of external trauma. It may serve as a mean of an objective documentation when forensic evidence is needed, particularly when sexual abuse of children is concerned (Figure 74). The examination includes the same techniques as the exam-



Figure 74. Objective documentation of anal trauma in a sexually abused child

ination of the vulva. Firm lateral pressure on both buttocks may evert the anal canal to some degree, to reveal the abnormality. Traction on the perianal skin also permits the examination of the lower anal canal. The perianal skin and the lower anal canal are first examined colposcopically before the application of 5% acetic acid. The field is soaked with 5% acetic acid, which remains to act at least 2-3 minutes to mark eventually present lesions. If this procedure causes burning, warm water rinsing should immediately be applied.

If numerous white lesions are present, anoscopy and proctoscopy should be performed. Using the proctoscope, views of the upper anal canal, the transition zone and the low rectal mucosa are readily obtained. Proctoscopy combined with a standard colposcopic technique including the application of acetic acid may be very difficult. Anaesthesia may be considered if such an examination is not tolerable by the patient in the outpatient setting.

The boundaries of the perianal epithelium and the anal canal are poorly defined. Perianal skin is that which can readily be seen on parting the buttocks. The anal canal epithelium is defined as the epithelium above this level and is limited cephaloid by the rectal mucosa (160). The normal perianal skin is unremarkable on colposcopy both before and after the application of acetic acid. The epithelium is heavily keratinized and responds to acetic acid only after prolonged soaking. Any changes present perianally may indicate the possible presence of similar lesions in the anal canal.

The anal canal may be involved by the extension of VIN from the perianal skin inwards to the linea pectinea and then the lesions are in continuity with the perianal ones. Alternatively, the anal mucosa can be isolately affected, without obvious connection with the vulva and the preineum. The colposcopy of the anal canal provides an excellent view of the anal cushions, the pectinate line and the transition zone. Spraying acetic acid onto the upper anal canal causes the transition zone to become more opaque and, hence, more obvious. The transition zone is usually located slightly cephaloid to the pectinate line, although its position varies from one individual to another. The transition zone becomes more obvious if mucus from the lower rectum is removed via proctoscope using a cotton swab. Mucus in

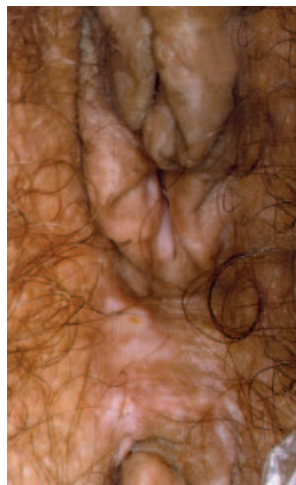


Figure 75. Lichen sclerosus on the perianal area

the anal canal or rectum may be misleading as it readily opacifies due to protein coagulation with the acetic acid. It is therefore essential to remove such mucus during the course of the anal colposcopy in order to see clearly the underlying epithelium and its response to acetic acid (160). Immature normal squamous epithelium may show slight acetowhite change, necessitating careful interpretation of anal colposcopy in patients who have recently undergone any anal surgery or who have anal symptoms such as pruritus ani.

There are three distinct sites where the lesions can appear: the perineum, anus and the anal canal. Lesions affecting the perineum and the anal region are basically similar to those on the vulva. Many of them show pigmentation and hyperkeratosis (Figure 75). Vascular changes usually seen on the cervix (punctations and mosaic) are not frequent perianally but may be seen in the anal canal. In the anal canal, the dysplastic epithelium may appear hyperemic on examination prior to the application of acetic acid. After the application of acetic acid such areas become more obvious.

The colposcopic features of papillomavirus infection and dysplasia in the lower anal canal and the perianal skin merge into each other. The colposcopic distinction between pure non-condylomatous HPV infection and low-grade AIN (1-2) is less accurate than in the colposcopic assessment of the cervix. Biopsy of any white lesion or abnormal vascularity is necessary because anoscopy and proctoscopy is inadequate in making a proper diagnosis. Most of postbiopsy bleeding can be stopped by pressure of at least 3 minutes.

### PERIANAL AND ANAL HPV INFECTION

In women, it is important to look for HPV infection and neoplasia as they usually affect a large area of the epithelium of the same origin. It extends backwards to the perianal region, anus and the rectal region. The source of infection, most likely, is the infected vulva. As on all other parts of the lower genital system, it can be clinical and subclinical.

**CLINICAL INFECTION** Anogenital warts may have very different appearance, from discrete small papules to large cauliflower growth (48). They are generally divided to condylomata acuminata and papular changes. Condylomata acuminata may be exuberant in the perianal region and their appearances are similar to those elsewhere (Figure 76-77). HPV induced papular lesions are smaller and less common. They can be pigmented



Figure 76. Perineal condylomata acuminata

or non-pigmented. They are more flat and not verrucous. Histologically, the HPV infection is evident.

**SUBCLINICAL INFECTION** Often appears around the anus and the perianal area. It is usually multicentric, affecting more sites. Colposcopic characteristics are equal to those for vulva and most often the lesions are visible as white fields after the application of acetic acid.

### ANAL INTRAEPITHELIAL NEOPLASIA AND INVASIVE CANCER OF THE ANUS

Anal intraepithelial neoplasia (AIN) is a potentially premalignant lesion found in the anal canal. It is a rare disease with a coincidental finding in 0.2-10.5% women with CIN (161). Anal intraepithelial neoplasia is a relatively recently recognized clinical entity and its prevalence malignant potential is a largely unknown. The histological description and grading of the morphologic changes seen in both the cervical and the anal canal lesions are similar, differing only in the degree of keratinization. Similar to other lower genital system neoplasia, AIN is divided into three grades: AIN 1, AIN 2 and AIN 3. AIN 1 and 2 are more often seen in younger patients, 19-43 (average 26) years old, while AIN 3 is present in women older than 40 years (162).

It has been shown that HPV has an important role in the aetiology of the majority of the perianal and anal cancers. It is pointed out that the transmission of the HPV along the genital system happens by direct spread from adjacent areas, i.e. from the vulva to the perianal and anal region (164). It has been demonstrated that 19% (7-20%) of women with CIN 3 have associated anal intraepithelial neoplasia (163). The aetiological role of HPV in anal cancer was reported as early as 20 years ago (165). In anal cancers, HPV 16 is the most frequently isolated type. In addition to HPV 16 positivity, smoking is identified as risk factor for anal intraepithelial neoplasia. Local trauma, human immunodeficiency virus (HIV) and depressed immune function (such as in renal transplants) are potential co-factors (166-169).



Figure 77. Perineal and perianal condylomata acuminata

Squamous carcinoma of the anus is an uncommon tumour that accounts for approximately 2% of cancers of the large bowel. It typically occurs in the elderly and previously used to be seen more frequently in women. However, there has been a striking incidence of this cancer in HIV-positive young men. Over 28% of women with anal placental carcinoma have the history of genital warts. In

69% of the anal tumours, originating from squamous and transitory epithelium, HPV DNA has been found, HPV 16 being the most frequent type, which was not found in the control group (170).

Unlike CIN, where the progression is expected in 36% over period of 20 years, the natural history of the perianal and the anal intraepithelial neoplasia is not well understood (171). Anal carcinoma is less frequent than cervical cancer and the rate of progression of AIN 3 to invasive cancer is substantially lower.



Figure 78. Perineal intraepithelial neoplasia

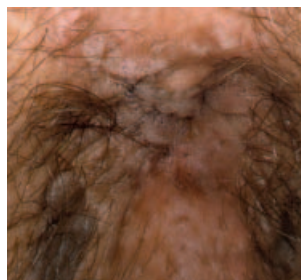


Figure 79. Perianal intraepithelial neoplasia

Clinically, the disease is similar to the intraepithelial disease of the vulva and often shows pigmentation of the perianal and anal epithelium (Figure 78). Perianal intraepithelial neoplasia occurs in two clinical forms: 1. as neoplastic transformation of macroscopic codylomata acuminata frequently unsuspected before the histologic examination and 2. as plaques of thick, keratotic, often discoloured perianal skin (Figure 79).

Although such lesions are generally visible to the naked eye, they are much better appreciated through the colposcope after the application of 5% acetic acid. (63). Vascular patterns that are seen on the cervix (punctations and mosaic) are not frequent on the perianal area but may be found in the anal canal.

Low-grade anal intraepithelial neoplasia was characterized by mild to moderate acetowhite change on colposcopy. No abnormal vessel patterns were observed. Half of these were incorrectly predicted by colposcopy as SPI (163). High-grade anal intraepithelial neoplasia in the anal canal is characterized by dense acetowhite change, sometimes occupying the full circumference.

Anal intraepithelial neoplasia can occur in continuity with vulvar disease, but also may appear as isolated lesions in the absence of vulvar changes. The colposcopist must be aware of the nature of this disease and the possible break in its continuity. The presence of perianal warts increase the chance for the presence of intraepithelial lesions in the anal canal. Fifty-seven percent of women with CIN and VIN have anal lesions

associated with HPV 16 (163). Therefore, each woman with HPV infection of the vulva must be colposcopically examined in detail, including the anus and the perianal area because cytological confirmation of the existence of these lesions is difficult due to the small number of cells obtained by cytological smear and their contamination with fecal contents (172).

It is difficult to distinguish early invasive lesions within high-grade AIN. Invasive cancer should be heaped up. Irregular, dense acetowhite epithelium, with dilated irregular vessels.

#### TREATMENT OF THE PERIANAL AND ANAL NEOPLASIA

Since AIN 1 and 2 lesions are unlikely to progress rapidly to AIN 3 or invasive disease, it seems appropriate that low-grade anal lesions should be managed in a similar manner to low-grade cervical and vulvar lesions. Such conservative strategy for the management of AIN 3 lesions may carry an unknown, though potentially significant risk of progression to invasive disease. Therefore AIN 3 lesions should be treated (160). Most surgeons use wide local excision, with an effort to obtain disease-free margins. Some authors have reported the advantages of ablative procedures such as laser ablation and cryotherapy. Microscopic disease found serendipitously in hemorrhoidectomy specimens can probably be treated conservatively with serial examinations alone. There is a lack of controlled data supporting an optimal treatment strategy. A multicenter controlled study comparing wide local excision with ablative procedures may be warranted (173).

The alarming increasing rate in ano-genital HPV infection in the sexually active population may herald a forthcoming dramatic increase in HPV associated cancers. If AIN 3 does carry significant invasive potential, an increase in the incidence of invasive anal squamous cell carcinoma may be expected.

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