Benign Lesions of the Vagina

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Abstract

This chapter describes the normal anatomy, histology and microflora of the vagina and a selection of benign vaginal diseases, including inflammatory and other disorders, with an emphasis on their etiopathogenesis and morphological features that may be necessary to achieve their correct diagnoses. Pathologic differential diagnosis is described in detail, especially in entities which can be confused with some premalignant or malignant diseases, such as malacoplakia, vaginal cysts and tumour-like lesions including fibroepithelial polyps, tubulosquamous polyps, postoperative spindle cell nodules and prolapsed fallopian tube. A discussion of vaginal adenosis is also included, including its historical perspective.

Keywords

Vagina · Benign diseases · Anatomy · Histology
Infectious diseases

9.1 Anatomy, Histology and Biostasis of the Vagina

9.1.1 Vaginal Anatomy and Histology

The vagina is an elastic, muscular, tubular structure which extends from the vestibule of the vulva to the uterus. It is located within the pelvis, posterior to the urinary bladder and anterior to the rectum. Its axis averages 30 degrees with the vertical and more than 90 degrees with the long axis of the uterus. The average length of the vagina in adults is about 9 cm; the anterior is shorter than the dorsal wall by about 3 cm, with the cervix filling the difference. During sexual arousal, the vagina expands in both length and width; its length and calibre are unrelated to symptoms of dyspareunia [1, 2]. It surrounds the exocervix and forms vault-like fornices between its cervical attachment and the lateral wall, which are deepest posteriorly. The anterior and posterior walls are in contact with each other, whereas the lateral walls remain fairly rigid and separated. This gives an H-shaped appearance to the vaginal canal in transverse sections.

Anteriorly, the vagina is in contact with the uterine cervix, the base of the bladder and the urethra. The urethra runs approximately one third of its length on the vagina, separated from the vagina by loose connective tissue, and then enters into the vaginal wall distally to become an inseparable part of vagina, with the fusion of their fasciae into a single dense layer.

Posteriorly, the upper fourth of the vagina is covered with peritoneum and forms the anterior part of the "cul-de-sac" or pouch of Douglas (rectouterine space). The adventitia of the middle half of the vagina is connected to the rectum by the rectovaginal septum. The lower fourth of the vagina is separated from the anal canal by the perineal body and anal and rectal sphincters. Laterally, the ureters run along both sides of the upper third of the vagina until entering the bladder wall. Distally, the vagina is partially surrounded by the levator ani and bulbocavernosus muscles and ultimately opens into the vestibule, situated beneath the urethra and between the inner margins of the labia minora.

The vasculature of the vagina is supplied by branches of the internal iliac artery: uterine, vaginal, middle rectal and internal pudendal arteries. Extensive arterial anastomoses provide an adequate blood supply, which minimizes the possibility of ischemic damage. The venous drainage forms a complex network, surrounds the vagina and communicates with the uterine, pudendal and rectal veins, which empty into the interior iliac veins.

The vaginal lymphatic system is complex and variable, with frequent crossovers between the left and right pelvis. The lymphatics of the upper anterior vagina and vaginal vault join those of the cervix and terminate in the medial chain of the external iliac lymph nodes, whereas the middle

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drains into internal iliac lymph nodes. The posterior portion of the vagina drains into the inferior gluteal, sacral and anorectal lymph nodes. The lymphatics of the distal vagina as well as the vulva drain into the femoral lymph nodes. It is important to note that, as a consequence of extensive anastomotic channels, any pelvic, anorectal or femoral node may be involved in the lymphatic drainage of any part of the vagina. In a simplified way, the tumours in the upper vagina can spread in a similar way to cervical carcinomas, and tumours in the lower vagina tend to involve superficial iliac and deep pelvic nodes, like vulvar cancer.

The nerve supply to the vagina is primarily derived from the superior hypogastric plexus of the autonomic nervous system. This plexus bifurcates and is joined by branches of the second through to the fifth sacral nerves, forming the pelvic plexuses. The upper part of the vagina is innervated by the uterovaginal plexus, and the lower vagina through the fibres of the pudendal nerve.

Histologically, the vaginal wall consists of three principal layers: the mucosa, muscularis and adventitia. The mucosa, on gross examination, forms ill-defined laterally oriented folds or rugae of about 2–5 mm thickness, which vary according to location and hormonal stimulation. The rugal pattern of the vaginal mucosa contributes to the organ's elasticity, and rugae are more prominent in nulliparous than in multiparous women.

The mucosa is lined by a non-keratinized glycogenated squamous epithelium (Fig. 9.1). The mature stratified squamous epithelium can be subdivided into several layers; basal, parabasal, intermediate and superficial. Mitoses are usually confined to the basal and parabasal layers, which are the active proliferative compartments. The basal layer consists of a single layer of columnar cells, with the long axis of the cells perpendicular to the basement membrane. The basal cells have scant cytoplasm and relatively large, oval and uniformly hyperchromatic nuclei. Occasional melanocytes are also found in about 3% of women. The parabasal layer usually consists of two to five layers of small cuboidal cells, with a centrally located, round and uniformly hyperchromatic nucleus. The intermediate layer is of variable thickness. The cells in this layer have moderate quantities of slightly flattened cytoplasm and oval nuclei with finely dispersed chromatin. The cells have variously prominent intercellular bridges, and the long cell axis of both nucleus and cytoplasm is parallel to the basement membrane. The superficial layer also varies in thickness. The cells are polygonal, contain abundant acidophilic cytoplasm and have an orientation similar to intermediate cells. Keratohyalin granules are sometimes seen in the cytoplasm. The nuclei are centrally located, small, round, hyperchromatic and pyknotic. In the intermediate and superficial cell layers, there may be present variable quantities of glycogen, which accumulates initially in a perinuclear location within intermediate cells, resulting in a clear zone around the nucleus. This appearance may resemble HPV changes with the perinuclear clearing (koilocytes), and the normal mucosal cells can be distinguished by having normal-sized nuclei and by their characteristic location in the middle rather than the superficial third of the epithelium. The normal vaginal mucosa lacks glands. The lamina propria (or submucosa) consists of a loose fibrovascular stroma with elastic fibres and nerves and a rich venous and lymphatic network. Superficially, beneath the squamous epithelium is a poorly defined zone containing atypical, large, stellate, polygonal or spindle stromal cells with scant cytoplasm. Some of these cells have multinucleated or multilobulated hyperchromatic nuclei. This band of stroma extends in an irregular fashion from the endocervix to the vulva, and these atypical stromal cells are thought to give rise to fibroepithelial polyps.

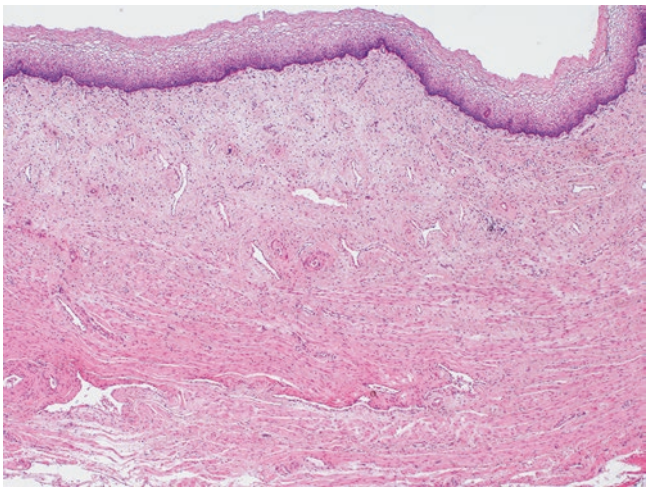

Fig. 9.1 Normal histology of the vagina. The mucosa is lined by non-keratinized squamous epithelium composed of basal layer, parabasal layers and glycogenated intermediate and superficial cells. Beneath the mucosa there is lamina propria, consisting of loose connective tissue with elastic fibres rich in venous and lymphatic vessels. In deeper part of the vaginal wall, there is muscularis, formed by loose bundles of smooth muscle cells

The muscularis consists of poorly delineated bundles of smooth muscle, forming the inner circular and outer longitudinal layers, continuous with the muscle layers of the uterus. Some of the outer longitudinal layers pass into the lateral pelvic wall and contribute to the inferior portion of the cardinal ligaments. The sphincter around the distal vagina is formed by the bulbospongiosus (bulbocavernosus) muscular fibres. The adventitia is a thin coat of dense connective tissue, containing the lymphatic and venous plexuses and nerve bundles. It joins with the loose connective tissue of the surrounding pelvis.

9.1.2 Steroid Hormone Effect on Vaginal Epithelia

Steroid hormones regulate the proliferation and differentiation of epithelial cells in the female genital tract. Their effect is primarily mediated through intranuclear steroid receptors. These receptors are present in all three layers of the vaginal wall, but the highest intensity of their expression is found in the squamous cells of the vaginal mucosa [3].

The thickness and maturation of the vaginal epithelium is mainly regulated by estrogen and varies throughout the menstrual cycle and throughout the various stages of the life cycle (birth, childhood, reproduction and the postmenopausal years). Vaginal epithelial receptors, particularly the estrogen nuclear receptor 1 (ESR1, formerly named ERα), integrate estrogen and growth factor signalling to mediate the switch between cell proliferation and differentiation [4]. Animal model investigations suggest that the proliferation and maturation of vaginal epithelium are mediated by the stromal estrogen receptors in a paracrine manner, whereas differentiation is promoted by epithelial estrogen receptors [4].

In the proliferative phase of the menstrual cycle, the epithelium progressively proliferates and matures fully in response to estrogens. This is reflected in a high expression of the proliferation marker Ki-67 coinciding with high serum estrogen levels [5]. During the secretory phase, higher levels of progesterone inhibit the maturation of the vaginal epithelium at the intermediate cell level, resulting in decreased thickness of the epithelium. Before puberty and after menopause, estrogenic activity is low or absent, and the vaginal epithelium fails to mature and hence remains thin. An exception to this can be seen in newborns where the vaginal epithelium is frequently mature because of the influence of placental estrogens, but it rapidly regresses to atrophy within about 4 weeks. Upon reaching puberty, in response to increased estrogen production by the maturing ovaries, the intermediate cell layer proliferates, and the superficial cells undergo maturation.

During the menopausal period, the changes in the vaginal mucosa are characterized by a gradual reduction in the thickness of the epithelium, loss of rugae and reduced tissue elasticity and lubrication. The decrease of estrogen hormones leads to the progressive loss of superficial cells, gradually followed by the decline and loss of intermediate cells, and finally the thinning of the epithelium leaves only six to eight layers of parabasal cells.

Vaginal atrophy could also be found in premenopausal women, where it is most commonly encountered either as a consequence of iatrogenic decrease of estrogen levels or during the postpartum period due to the loss of placental estrogen and the antagonistic action of prolactin on estrogen production during lactation [6].

Atrophy can cause some local symptoms of vaginal dryness, itch, discomfort, symptomatic prolapse, change in vaginal discharge or dyspareunia. Local or systemic exposure of the atrophic mucosa to estrogen leads to maturation of squamous cells, and thus the same level of maturation similar to the proliferative phase of the menstrual cycle could be achieved.

Estrogen also affects the maintenance of vaginal smooth muscle bundle density, growth and the functions of vascular and nonvascular smooth muscle in the subepithelial vaginal layers and nerve ending morphology as well as their density. In addition, estrogens have been shown to enhance genital sensation and play a role during sexual arousal. In the early phases of sexual response, the proximal two thirds of the vagina lengthen and increase in volume, followed by constriction of the distal third [2]. Estrogens also affect the genes involved in the immune response and many other factors involved in maintaining a healthy condition and moisture in the vaginal mucosa. Vaginal lubrication typically results from increased vascular pressure and genital engorgement caused by dilatation of the vaginal vasculature in response to excitatory stimuli (mediated by hormones, particularly estrogen, neurotransmitters and nitric oxide) [7]. The fluid is usually acidic (pH around 4.6) and contains a variable amount of antibodies, enzymes and their inhibitors, which may play a role in the liquefaction of coagulated semen and the capacitation of spermatocytes or have antimicrobial activity [8].

9.1.3 Biostasis of the Vagina

The vagina and its microbiota form a balanced ecosystem, which plays an important role in preventing colonization by pathogenic organisms, including those responsible for bacterial vaginosis, sexually transmitted and urinary tract infectious agents. The ecosystem reflects a delicate balance which includes the interplay of steroid hormones, vascularity, vaginal acidity and glycogen [8]. This can easily be disturbed by chemical, mechanical or hormonal manipulation. The vaginal flora is a dynamic and closely interrelated system comprised of a vast diversity of microorganism species (more than 200 bacterial species, dominated by *Lactobacillus* spp.), which varies and changes from birth through menarche to menopause [9]. Initial colonization at birth comes from the vaginal microbiota or from the skin or mouth microbiota of the mother. Before menarche the vagina is colonized by diverse assemblages of enteric and skin species of microorganisms, and the pH of the vagina is nearly neutral [10]. Around the start and during the reproductive phase of women's lives, hormonal changes trigger certain changes in the spectrum of bacterial species. The increased estrogen levels support the proliferation of the vaginal epithelium and the

intraepithelial production of glycogen, whereas progesterone causes the cytolysis of epithelial cells and the release of glycogen. The glycogen and its breakdown products are metabolized by lactobacilli and other bacteria to lactic acid, leading to acidification of the vaginal microenvironment to pH of 3.8–4.4, which is defined as normal [9]. After menopause, the decreasing estrogen levels lead to the altered composition of the vaginal microbiota.

The importance of lactic acid-producing bacteria in the vagina was discovered by Albert Döderlein in 1892. *Lactobacillus* spp. are a group of Gram-positive, anaerobic bacteria that produce lactic acid as a by-product of glycogen fermentation and serve as a natural resistance factor against potentially pathogenic microorganisms. The production of lactic acid maintains the low vaginal pH and so creates an unsuitable environment for pathogenic microbial species such as *Trichomonas vaginalis* and *Candida* spp. [11]. Other defensive mechanisms include competitive adhesion to the vaginal epithelium, production of antibacterial substances (bacteriocins) and hydrogen peroxide and the interactions between the plasminogen-plasmin system and the local immune system [11]. Maintaining a high number of lactic acid bacteria is regarded as a hallmark of health. The disruption of the vaginal ecosystem may cause various diseases and is also associated with an increased risk of infection, including but not limited to human immunodeficiency virus infection [11].

9.2 Inflammatory Disorders of the Vagina

The normal vaginal flora is varied and constitutes a dynamic ecosystem known as the vaginal microbiota, which is delicately balanced and influenced by factors such as vaginal acidity, glycogen, vascularity and the interactions of steroid hormones [12]. Although the make-up of vaginal flora changes from birth throughout the reproductive life and menopause, the predominant microorganisms in a healthy vaginal environment are represented by *Lactobacillus* species. These species are not only able to colonize the vaginal mucosa but, more importantly, produce antimicrobial substances which act to prevent the growth of pathogenic microorganisms [13].

Urogenital infections, especially in premenopausal women, represent an important female health problem as they often require antibiotic treatment and their recurrence and relapse rates tend to be high.

Vaginitis

Vaginitis is an inflammation of the vagina characterized by the presence of inflammatory response consistent with alterations in the vaginal ecosystem (Fig. 9.2). In contrast, the term *vaginosis* is, strictly speaking, used to describe an altered vaginal ecosystem with reduced beneficial vaginal lactobacilli but a demonstrable absence of inflammatory response [14]. The three most prevalent diagnoses comprising 70% of all reported cases of vaginitis include bacterial vaginosis (BV), trichomoniasis and vulvovaginal candidiasis (VVC) [15]. Another significant condition is represented by a recently recognized entity called aerobic vaginitis.

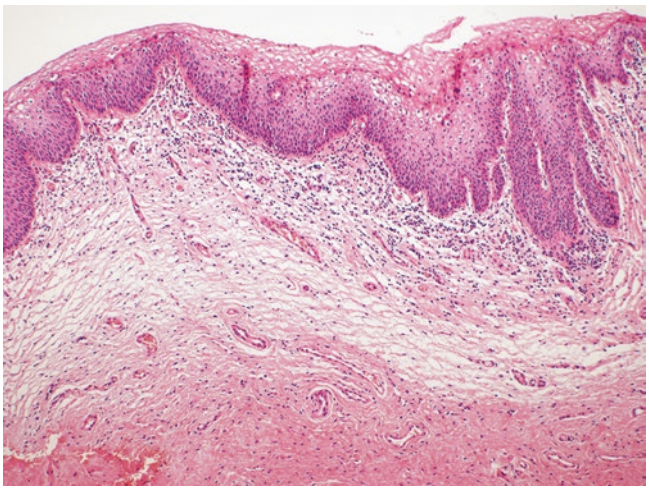

Fig. 9.2 Chronic nonspecific vaginitis. The mucosa is covered by normal stratified squamous epithelium. There is a mild inflammatory (predominantly lymphocytic) infiltrate in the lamina propria

Vaginitis is primarily a clinical diagnosis based on the presence of subjective symptoms of various kinds of discomfort (pruritus and pain being among the most frequent complaints) and the presence of a vaginal discharge, although building the diagnosis on discharge alone may at times lead to overdiagnosis [12]. What is commonly termed "vaginal discharge" often includes not only the pathological discharge caused by vaginitis but also simply the increased production of vaginal fluid, which can be frequently observed in the middle of the menstrual cycle when the cervical and uterine mucus become rather watery and profuse. It is therefore important to take into account the typical signs pointing to a vaginitis-associated discharge, such as the odour, colour, consistency and quantity of the discharge.

9.2.1 Bacterial Infections

9.2.1.1 Bacterial Vaginosis

Bacterial vaginosis (BV) is the most common cause of acute vaginitis. It is described as a polymicrobial disorder accompanied by an increase in the vaginal pH to over 4.5, reduced or absent lactobacillus colonization and overgrowth of several facultative and obligate anaerobic bacteria (Fig. 9.3) [16]. A large number of studies have demonstrated that despite its generally mild clinical presentation, bacterial vaginosis is associated with a variety of adverse pregnancy outcomes, such as miscarriage, preterm delivery of a low-birth-weight infant, premature rupture of the membranes,

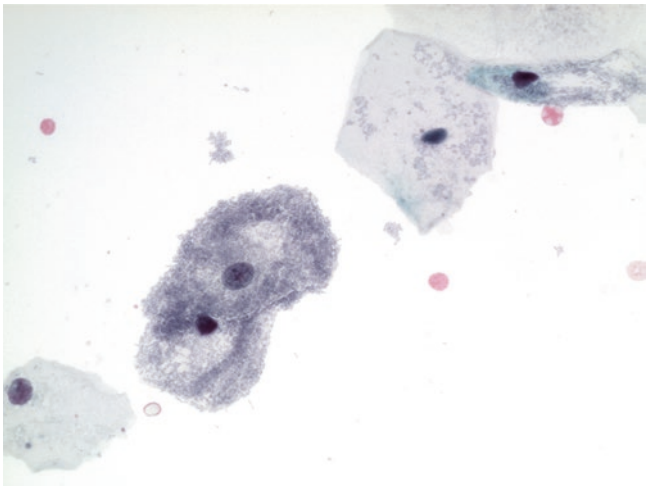

Fig. 9.3 Bacterial vaginosis. Typical clue cells can be seen, consisting of squamous cells covered by bacteria (in this case *Gardnerella vaginalis*)

chorioamnionitis, amniotic fluid infections and post-caesarean endometritis [17–20]. Bacterial vaginosis has also been reported to increase the risk of contracting a sexually transmitted disease, including an increased susceptibility to the human immunodeficiency virus [17, 20]. Other gynaecological complications include pelvic inflammatory disease, tubal infertility, postoperative infections and cervicitis [21].

Bacterial vaginosis is characterized by a thin, watery, fishy-smelling discharge, positive "amine" odour test (which can be easily demonstrated by adding 10% potassium hydroxide solution to a drop of vaginal discharge on a slide, with the resulting production of volatilized amines causing the distinctive odour) and a wet mount showing >20% clue cells (vaginal epithelial cells with a large number of attached bacteria) [22]. The underlying cause of bacterial vaginosis is described as a shift in the balance of the vaginal microflora with a reduction in lactobacilli and an increase in facultative and anaerobic bacteria (in either their number and/or type) [23]. This bacterial overgrowth can be caused by a number of anaerobic and other bacteria, primarily represented by *Gardnerella vaginalis*, *Mobiluncus* spp., *Prevotella* spp., *Bacteroides* spp., *Streptococcus* spp., *Megasphaera* spp., *Ureaplasma urealyticum*, *Atopobium vaginae* and *Mycoplasma* spp. [17, 21, 24].

Bacterial vaginosis can be diagnosed either based on the clinical Amsel's criteria or by the Nugent method, which has become the gold standard for histopathological diagnosis [25, 26]. Clinical diagnosis requires the fulfilment of at least three of the four main features described above (vaginal pH > 4.5, specific discharge, positive "amine" odour test and the presence of >20% clue cells on the wet mount). One of the shortcomings of using clinical criteria is that these cannot be applied to postmenopausal women, as the vaginal pH of these patients is constantly elevated above 4.5 due to the lack of hormonal stimulation and estrogenization of the vaginal mucosa (which lacks the glycogen deposits needed by the lactobacilli and these in turn cannot proliferate and produce lactic acid and hydrogen peroxide in the process). The amount of discharge in these women can also pose a problem, because vaginal discharge tends to be scarce, which makes judging its quality and quantity difficult [16].

The Nugent method was first suggested at the beginning of 1990s as a part of the Vaginal Infection and Prematurity Study [26]. The score is based on interpreting Gram-stained smears of the vaginal discharge, working under the assumption that the vaginal ecosystem of normal, healthy women is fully colonized by lactobacilli. The Nugent method quantitatively evaluates three different morphotypes: (1) lactobacilli, (2) *Gardnerella*-like species (*Gardnerella vaginalis*, *Bacteroides* spp., *Prevotella* spp., *Porphyromonas* spp.) and (3) *Mobiluncus* spp. in five different fields under oil immersion (magnification ×1000). The average number of lactobacilli morphotypes (large Gram-positive rods), *Gardnerella*-like morphotypes (small Gram-variable rods) and *Mobiluncus* spp. morphotypes (small, curved Gram-variable or Gram-negative rods) in five fields is established and then ranked. The points assigned to each morphotype are then combined, and the sum represents the patient's final Nugent score, which classifies the vaginal flora as normal (Nugent score 0–3), intermediate altered flora (Nugent score 4–6) and full-blown bacterial vaginosis (Nugent score 7–10) (Table 9.1).

However, given the differences between vaginal flora in fertile, perimenopausal and postmenopausal women, it has been suggested that the Nugent score system is inadequate for evaluating the normal and intermediate vaginal flora in women over the age of 40 years [16]. Due to the physiological decrease in lactobacillus colonization during the peri- and postmenopausal period, it is quite common for the vaginal flora of these patients to show an absence of lactoba-

Table 9.1 Nugent scoring system for Gram-stained vaginal smears for the diagnosis of bacterial vaginosis [26]

Score	*Lactobacillus* morphotype	*Gardnerella*-like spp. morphotypes	Curved Gram-variable rods
0	>30	0	0
1	5–30	<1	<1, 1–4
2	1–4	1–4	5–30, >30
3	<1	5–30	
4	0	>30	
Final Nugent Score (NS): the sum of the scores for the presence of *Lactobacillus*, *Gardnerella*-like morphotypes and curved Gram-variable rods			
NS 0–3: normal vaginal flora			
NS 4–6: intermediate altered flora			
*NS 4**: intermediate abnormal flora (acc. to Cauci et al.) [16]			
NS 7–10: bacterial vaginosis			

cilli morphotypes without an increase in bacterial vaginosis-associated microorganisms. It has therefore been proposed that, when dealing with this specific age group, the mere absence of lactobacilli morphotypes (without the accompanying limited overgrowth of *Gardnerella*-like and *Mobiluncus* spp.) should not be assigned the Nugent score of 4, but a score of 4*, and this special kind of mixed flora should be termed "intermediate abnormal flora".

Nevertheless, due to the high percentage of women with bacterial vaginosis who are asymptomatic, the Nugent scoring method cannot be always utilized. In such cases the use of a Pap smear was suggested as a suitable test for diagnosing bacterial vaginosis, with the sensitivity of 78% and specificity and positive predictive value of 86.9% [27]. Although the cervicovaginal smear is an effective tool, the Bethesda system for reporting the results only recognizes one category—"shift in vaginal flora suggestive of bacterial vaginosis"—and studies have therefore proposed utilizing the 1988 Dutch coding system (KOPAC), which differentiates between two categories: "dysbacteriosis O3" (clue cells with coccobacilli in the background) and "*Gardnerella vaginalis* O5" (blue mountain cells completely covered by a mountain of blue-staining round bacteria) [28]. Given the clinical significance of pure *Gardnerella* infection, the distinction between simple dysbacteriosis and *Gardnerella* infection is very desirable.

9.2.1.2 Aerobic Vaginitis

Aerobic vaginitis (AV) is an infectious entity which was first officially recognized by Donders et al. in 2002 as a condition characterized by abnormal (dysbiotic) vaginal microflora, which is different from bacterial vaginosis and thus represents an individual entity [29].

The diagnostic criteria of bacterial vaginosis have now been firmly established, with the Nugent score providing a clear definition of normal microflora (Nugent score of 3 or less) and a full-blown case of BV (Nugent score of 7–10). It is the category between these two marginal groups, called intermediate altered microflora, which has proved to be somewhat problematic in respect to establishing what exactly defines this altered state. This particular type of microflora, together with the varying degrees of associated vaginal atrophy and inflammation (unlike the suppressed immune response typical for bacterial vaginosis), was therefore called aerobic vaginitis [30]. The prevalence of aerobic vaginitis is reported to be between 8.3 and 10.8% of pregnant women and between 5.0 and 23.74% in symptomatic non-pregnant women [31]. The most severe presentation of aerobic vaginitis is comparative to desquamative inflammatory vaginitis [32].

Similarly to bacterial vaginosis, aerobic vaginitis also results from a shift in the balance of the vaginal microbiota. The altered microflora in aerobic vaginitis consists of commensal aerobic microorganisms of intestinal origin, comprised of *Escherichia coli*, *Staphylococcus aureus*, *Enterococcus faecalis*, group B *Streptococcus* (*S. agalactiae*) and coagulase-negative staphylococci such as *Staphylococcus epidermidis* [29]. Clinical symptoms of aerobic vaginitis include a typical vaginal discharge, introital and vaginal redness, dyspareunia in some (especially long standing) cases and subjective complaints of stinging and burning sensations. The discharge in aerobic vaginitis differs from the one typical for bacterial vaginosis—it shows a typically purulent character with high viscosity, yellowish or greenish colour, homogenous consistency and foul-smelling rotten odour (but no fishy smell). Due to the epithelial disruption, the vaginal mucosa appears red and inflamed on macroscopic examination, and in severe cases erosions, ulcerations and ecchymotic bleeding may be present. The severe cases may also involve cervix, which then exhibits similar superficial erosions and ulcerations, hyperemia and scattered ecchymotic bleeding [33].

The recommended diagnostic method is a wet mount microscopy of the vaginal fluid, using a scoring system similar to the one in bacterial vaginosis in order to categorize the vaginal microflora into normal microflora and light, moderate and severe case of aerobic vaginitis [29, 30]. The AV score is composite and consists of lactobacillary grade, number of leucocytes, proportion of toxic leucocytes (leucocytes with toxic granulation), background microflora and proportion of parabasal cells. Each of these criteria is assigned points: 0 for absent, 1 for moderate and 2 for severe. The final AV score is then calculated by adding these points. The score of 0–2 means no aerobic vaginitis, 3–4 means light aerobic vaginitis, 5–6 means moderate vaginitis and a score of 7–10 corresponds to severe aerobic vaginitis (Table 9.2).

The most important characteristics distinguishing aerobic vaginitis from bacterial vaginosis, from the view of a pathologist, include the presence of various degrees of mucosal inflammation (severe cases with scattered bleeding points or ulcers) and severely depressed lactobacilli on wet smears (with the presence of chains of cocci, numerous leucocytes, toxic leucocytes and parabasal cells). There are also specific findings in the Gram stain (deficiency of lactobacilli with increased levels of Gram-positive bacteria and Gram-negative small rods from *Enterobacteriaceae*) [33].

Aerobic vaginitis is associated with several significant clinical implications. Firstly, it is often found mixed with other vaginal infections, namely, vulvovaginal candidiasis, bacterial vaginosis and trichomonal vaginitis, resulting in atypical complaints and symptoms which may make the syndromic diagnosis problematic [34, 35]. Secondly, aerobic vaginitis has been associated with various adverse pregnancy outcomes such as increased risk of preterm delivery, premature rupture of fetal membranes, chorioamnionitis and funisitis of the fetus [30, 32].

Table 9.2 The scoring system for the diagnosis of aerobic vaginitis [29, 30]

Sub-score	LBG	No. of toxic leucocytes	Proportion of toxic leucocytes	Background flora	PBC
0	I, IIa	≤10/hpf	None or sporadic	Unremarkable or cytolysis	None or < 1%
1	IIb	>10/hpf and ≤ 10/epithelial cell	≤50% of all leucocytes	Small coliform bacilli	≤10%
2	III	>10/epithelial cell	>50% of all leucocytes	Chains or cocci	>10%
Sub-score: 0 points (criterion absent), 1 point (moderate), 2 points (severe)					
Final AV score: *0–2* means no signs of aerobic vaginitis, *3–4* light aerobic vaginitis, *5–6* moderate aerobic vaginitis and *7–10* severe vaginitis					
PBC—proportion of parabasal cells					
LBG—Lactobacillary grade					
I	Normal vaginal microflora, containing mostly lactobacillary cell types with no or very few coccoid bacteria				
II	Diminished numbers of lactobacilli mixed with other bacteria				
	IIa—slightly disturbed microflora				
	IIb—moderately disturbed microflora				
III	No lactobacilli, microflora is dominated by numerous other bacteria (cocci, anaerobic coccobacilli or small bacilli)				

9.2.1.3 Streptococcus Group B

Group B streptococci (GBS), or *Streptococcus agalactiae*, are considered to be a normal part of the vaginal microflora and as such non-pathogenic in the vagina [36]. Reports suggest that at least 25% of women are regularly colonized with GBS in the vagina and rectum [22]. So far no specific histopathologic changes descriptive of GBS vaginitis have been described.

Unlike the case of GBS vaginitis, GBS morbidity among the obstetrical population is well established. Cervicovaginal colonization with group B streptococci at 23–26 weeks' gestation is associated with an increased risk of preterm birth and delivery of a low-birth-weight infant, while colonization at delivery shows association with neonatal sepsis, although the exact factors determining the risk of developing such complications are still unknown [37]. Other reported complications include intraamniotic infection and endomyometritis [38]. *Streptococcus agalactiae* is also responsible for a number of serious infections in newborns of colonized mothers, including pneumonia, meningitis and septicaemia [39].

9.2.1.4 Streptococcus Group A

Group A beta-haemolytic streptococci (GAS), or *Streptococcus pyogenes*, are an established cause of cellulitis, necrotizing fasciitis, erysipelas, impetigo and puerperal infections. Aside from the well-known soft tissue and skin infections, *Streptococcus pyogenes* also represents one of the rarer causes of vaginitis.

Group A streptococcal vaginitis is usually encountered in prepubescent girls, although reports of findings in adult women are increasing [40, 41]. Clinical symptoms of GAS vulvovaginitis are usually acute and more severe than the signs caused by other types of vaginitis [42]. The most common complaints include vulvar and vaginal pain, often spreading to the perianal regions, pruritus and dyspareunia. The discharge associated with GAS infection is typically copious, malodorous (foul-smelling, with absence of the fishy smell characteristic of BV), yellow and seropurulent in consistency. Vaginal walls may display a marked oedema and erythema.

The diagnosis is usually made by correlating the clinical signs and symptoms with the results of a wet mount and Gram stain and can be confirmed by a culture with overgrowth of group A streptococci. Both wet mount and Gram stain of a vaginal smear usually show numerous polymorphonuclear leukocytes, singlets, doublets or chains of Gram-positive cocci and the absence of lactobacilli [41].

9.2.1.5 Toxic Shock Syndrome (TSS)

Toxic shock syndrome (TSS) is a potentially fatal, acute systemic illness caused by an infection with *Staphylococcus aureus* strains producing toxic shock syndrome toxins (TSST-1) or by *Streptococcus pyogenes* M types I and III (group A beta-haemolytic streptococcus, GABHS) capable of producing streptococcal pyrogenic exotoxin A (SPeA), streptococcal pyrogenic exotoxin C (SPeC), protein cysteine SPeB, mitogenic factor (MF, SPeF) and streptococcal superantigen (SSA) [43, 44]. The interaction of these toxins with the immune system of the host leads to a massive release of pro-inflammatory cytokines including TNF-α, TNF-β, IL-1, IL-2 and IL-6, which are responsible for the severe shock response and resulting organ failure.

Toxic shock syndrome can be divided into menstrual and nonmenstrual cases. The menstrual cases are typically found in the adolescent and fertile female population and are associated with vaginal colonization by *S. aureus*, while the nonmenstrual cases are common in postmenopausal women, men and children [44, 45]. Recently, a relationship between the vaginal microbiota and the risk of TSS has been proposed, suggesting that women with aerobic vaginitis (colonized by *Streptococcus agalactiae* and *Enterococcus* spp.) may be more susceptible to menstrual toxic shock syndrome as the presence of these bacteria significantly induces TSST-1 production [46]. Staphylococcal TSS was first described in

the 1980s among young American women using superabsorbent tampons [47]. It is generally more common than streptococcal, which is however reportedly increasing in frequency and characterized by a poor outcome and mortality rate as high as 80% [43, 48, 49].

9.2.2 Fungal Infections

9.2.2.1 Vulvovaginal Candidiasis

Vulvovaginal candidiasis (VVC) is a fungal disease predominantly caused by *Candida albicans*, which is responsible for up to 65–90% of vaginal *Candida* spp. infections, with the non-albicans *Candida* species being responsible for up to 30% of infections [24]. The most common non-*Candida* species found in the vaginal isolates, in descending order, are *C. glabrata*, *C. tropicalis*, *C. parapsilosis* and *C. krusei*. Their clinical significance is given by the fact that while *C. albicans* remains sensitive to azole treatment, non-albicans *Candida* species have shown fluconazole resistance [50–52]. The emergence of *C. glabrata* has been a special cause for concern, as its incidence has been increasing continually since the first reports of a few rare cases in the 1990s [53].

Vulvovaginal candidiasis caused by *Candida* spp. is the second most common vaginal infection, and, according to statistics, up to 70–75% of women of a reproductive age will suffer from at least one clinical episode of VVC [15, 54, 55].

The development of a symptomatic infection first requires the colonization of the vagina with *Candida* spp., which usually occurs by a local introduction of the organism from the perineum and perianal areas through digital or sexual contact. Following the contact, *Candida* adheres to the vaginal epithelium and causes either asymptomatic colonization or, when it switches from its yeast cell morphology to its hyphal form, leads to VVC [56]. The literary prevalence of colonization in asymptomatic women varies, with positive vaginal cultures of *Candida* species being found in 15–37% of asymptomatic women [50]. In a healthy host, there is a balance between *Candida* spp. and the other microorganisms forming the vaginal microbiota, and *Candida* is therefore considered as a commensal organism, well tolerated in low numbers. This balance in the vaginal ecosystem can become disturbed in a number of situations. The predisposing factors include uncontrolled diabetes mellitus (and the role of glycosuria in promoting *Candida* colonization), frequent antibiotic use, high-estrogen oral contraception, hormone replacement therapy and immunosuppression [15, 57].

Typical clinical symptoms of acute VVC include mainly the characteristic vaginal discharge, which is non-malodorous and of a cheesy or curd-like consistency and colour [14]. The most common subjective complaints are of intense vulvar itching, soreness, superficial dyspareunia and dysuria. The gross macroscopic findings include oedema, reddened and erythematous mucosa with possible fissuring and satellite skin lesions.

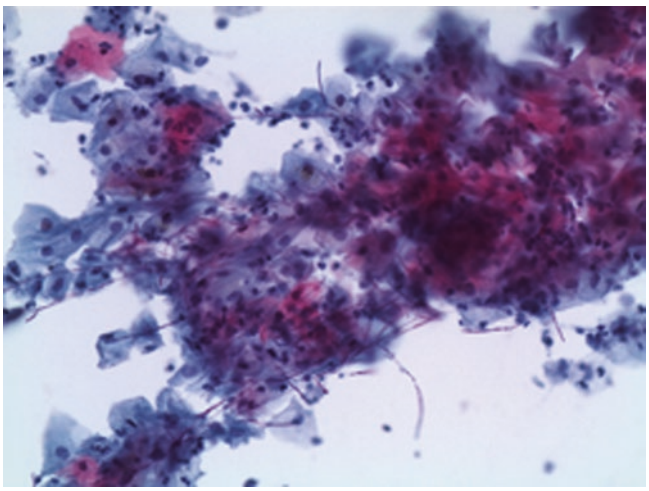

Fig. 9.4 Candida albicans. Numerous yeast and pseudohyphae are present, intermingled with superficial squamous cells (cytology specimen; Papanicolaou staining)

The microscopic diagnosis can be based on an examination of a cytology specimen or wet mount of the discharge or a Gram stain (Fig. 9.4). The presence of blastospores and pseudohyphae is diagnostic of VVC, although their morphologic appearance is not entirely specific and the reported sensitivity of the wet prep exam is only about 65% [12]. Biopsy samples are used rarely in diagnosing vulvovaginal candidosis, but if they are available the main microscopic findings include marked acute neutrophilic infiltration of the epithelium, predominantly mononuclear inflammation and congested blood vessels in the stroma and reactive changes of the squamous epithelium [12, 22]. The superficial layers of the squamous epithelium may show adhering desquamated epithelial cells, which can be intertwined with identifiable pseudohyphae (long, tube-like filaments arranged in parallel with constrictions between the individual cells).

9.2.2.2 Actinomycosis

Actinomyces is a Gram-positive, non-spore-forming, nonmotile and non-acid-fast anaerobic bacterium, which is found as a normal commensal organism in the oral cavity, respiratory tract and gastrointestinal tract. The vagina of up to 27% of healthy, asymptomatic women may also be colonized [22, 58]. The most commonly encountered member of the *Actinomyces* genus is *Actinomyces israelii*, with other relatively common species being *Actinomyces turicensis* (isolated in up to 18.5% of clinical cases of actinomycosis and recently reported as the cause of systemic bacteraemia in a patient with pyometra), *A. naeslundii*, *A. viscosus* and *A. bovis* [59, 60]. The colonization of the vaginal flora is considered to follow a transfer of the organism from the intestine, and infection is usually initiated if there is a local breach

of the mucosal barrier. In the pathologic setting, *Actinomyces* has been associated with infections of mainly the female upper reproductive tract (cervicitis, endometritis, tuboovarian and pelvic abscesses); however there was also a reported case of a rare primary involvement of the vulva [58]. Actinomycosis of the female genital tract has a significantly higher prevalence in women with long-lasting intrauterine contraceptive devices [12]. The estimated prevalence of *Actinomyces israelii* infection among women with IUDs is reportedly between 1.6 and 11%, with a strong positive association with the duration of application and with plastic devices without a hormonal or metal load [61]. The length of time the device has spent in the uterine cavity before the development of an infection is variable, but up to 85% of cases reportedly occur after 3 or more years [62].

Actinomycosis of the vagina is uncommon, but it may be observed in women with intravaginal foreign bodies (such as IUDs or suture material). The presence of foreign bodies is considered to enable the overgrowth of actinomycetes and cause vaginitis. The infection is characteristic by its slow, but continuous, progress across anatomical sites leading to the formation of extensive granulomatous, suppurative abscesses which may cause perforations of the skin and drain via multiple sinus tracts. The abscesses are usually surrounded by copious granulation tissue and abundant dense, fibrous scar tissue [63]. If the perforation involves any of the surrounding abdominopelvic organs, fistulas may form between the affected organs. The draining pus contains multiple small, soft yellowish so-called sulphur granules which consist of branching aggregates of the organisms, but are not specific for actinomycosis as they can also be observed with *Nocardia* and fungal infections [64]. The presence of sulphur granules (also called Gupta bodies or actinomycotic drusen) indicates a local tissue reaction to the infection [58].

The clinical presentation associated with infection includes postcoital bleeding, malodorous vaginal discharge, pruritus and in case of abdominopelvic abscesses abdominal pain [22].

The diagnosis of genital actinomycosis may be a difficult one, as the clinical signs are often nonspecific and the use of Papanicolaou-stained cytologic slides reportedly lacks specificity and sensitivity and has a low positive predictive value—for example, in one study of women with actinomycotic abscesses, only half of those with an available Pap smear test were positive for *Actinomyces* [64].

Microscopically, Pap smears typically show the presence of inflammatory cells and characteristic collections of fine, filament-like blue bacterial structures radiating from a dense, basophilic central core [61]. Additional Gram stain and Gomori methenamine silver stain may be used to confirm the presence of *Actinomyces* and distinguish it from pseudoactinomycotic radiate granules that are noninfectious and a common finding in women with intrauterine devices [62]. Pseudoactinomycotic radiate granules (PAMRAGs) are composed of neutral glycoproteins, lipids and calcium, often showing lamination in the centre ("tidewater" marks) and club-like peripheral projections (Fig. 9.5) [65]. They are a specific form of a tissue response to the presence of an IUD and may be frequently found on their own in the absence of an *Actinomyces* infection or sometimes can be identified in the surroundings of actinomycotic sulphur granules.

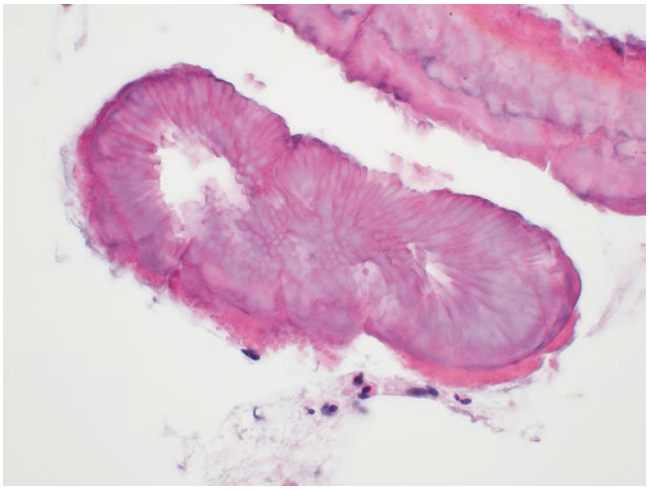

Fig. 9.5 Pseudoactinomycotic radiate granules (PAMRAGs). Note the club-like peripheral projections

Although the finding of sulphur granules surrounded by pus is highly suggestive of actinomycosis, the gold standard for diagnosis remains to be culture, which is unfortunately a lengthy procedure as *Actinomyces* are a fastidious and slow-growing species [66].

9.2.3 Protozoal Infections

9.2.3.1 Trichomoniasis

Trichomoniasis is the most common non-viral, curable sexually transmitted infection in the world [24]. It is caused by *Trichomonas vaginalis*, a flagellated protozoan parasite of the human reproductive system [67]. This extracellular, facultatively anaerobic and obligatory sexually transmitted microorganism is uniquely adapted to the epithelial lining of the human vagina, uterine cervix and both the male and female urethra [68]. In women, *Trichomonas vaginalis* infection may be relatively asymptomatic, but it usually presents as vaginitis and/or cervicitis, while in men it tends to be asymptomatic in the majority of cases.

The most common gynaecologic complications of trichomoniasis include endometritis, adnexitis, pyosalpinx and atypical pelvic inflammatory disease [69]. Trichomoniasis has also been linked to various adverse pregnancy outcomes including premature rupture of membranes, preterm birth and low birth weight [70].

The most common clinical symptoms in women include abnormal vaginal discharge, pruritus, vaginitis, cervicitis, urethritis and dyspareunia [71]. The discharge is usually diffuse, yellow to green in colour and malodorous, often with an increase in vaginal pH (>5). On macroscopic examination the vaginal mucosa is erythematous and may show numerous variable punctate haemorrhages, which led to the term "strawberry cervix" (*colpitis macularis*) and can be observed in about 5–50% of women [72]. Due to the variability of the clinical presentation and similarity to a number of other STDs, the diagnosis cannot be based purely on the symptoms. This conclusion is further supported by the fact that the characteristic presentation implicating *T. vaginalis* (inflamed mucosa with numerous punctate ecchymoses and a frothy discharge) is reportedly present in only about 2% of cases [67].

The gold standard for diagnosis of trichomoniasis is still considered to be the identification of trichomonads by culture in Diamonds medium. However, the cultures require an incubation time of 7 days (although some signs of growth can already be observed after 48 h), which is not desirable in a clinical setting where the proper treatment needs to be administered without unnecessary delay. The alternatives to cultures include the visualization of trichomonads on wet mount and microscopy, combined with a positive whiff test and a vaginal discharge pH of >4.5 [14].

The wet mount of a saline preparation of the vaginal (or cervical) discharge allows for identification of the motile organisms, which are visible as ovoid shapes about 10–20 μm in diameter, with polar flagella which provide the typical jerky swaying motion [12]. This method is simple, easy to access and very cost-effective. Unfortunately, studies show that the sensitivity of microscopic evaluation is rather low (around 60%) and further decreases in cases when there is a delay between the sample acquisition and evaluation, due to the reduction in parasite motility, making it harder to identify. A delay of as little as 10 min can decrease the sensitivity by further 20% [67]. It is also possible to use the Pap smear test, where the organisms appear as pear-shaped cells with a "lancet"-shaped nucleus and red cytoplasmic granules, but its sensitivity for diagnosis is also considered to be poor [22].

Biopsy specimens are uncommon, and if used the organisms are not directly detectable, although there is a variety of inflammatory and reactive changes which may point to their presence. The vaginal squamous epithelium may be spongiotic, with numerous neutrophils which can sometimes form intraepithelial abscesses. The epithelium may show irregular acanthosis with pseudoepitheliomatous hyperplasia. The submucosa often exhibits an inflammatory response, with hyperaemia and a dense, nonspecific chronic inflammatory infiltrate composed predominantly of lymphocytes and plasmocytes [12, 22].

With the wide range of emerging molecular technology methods, providing superior sensitivity and specificity when compared with wet mount examination, the preferred diagnostic methods are shifting towards PCR-based essays and commercially available nucleic acid amplification tests (NAATs). A standard PCR essay was reported to have a sensitivity of 97% and specificity of 98%, and the same authors also mention that the sensitivity of wet mount microscopy in their study reached only 36%, while the sensitivity of culture reached 70% [73].

Recently, immunocytochemistry (ICC) was suggested as another possible diagnostic method, which could be more accessible in the clinical setting of developing countries (where the trichomoniasis epidemic seems to be most pronounced) than the modern techniques of nucleic acid amplification tests (NAATs) and PCR-based essays [74].

9.2.4 Viral Infections

9.2.4.1 Herpes Simplex Virus

Herpes simplex virus (HSV) is one of the most prevalent sexually transmitted infections with an estimated more than 500 million adults globally infected with either HSV type 1 or 2 [75]. In the United States alone, there are approximately 750,000 new cases of genital herpes every year, with a prevalence of 20 million cases [76]. The majority of the genital tract infections have traditionally been caused by the type 2, although HSV-1 is becoming increasingly more common [77]. Most of the cases are clinically asymptomatic, and intermittent asymptomatic viral shedding can occur with genital HSV-2 infection [78].

The classical case of primary symptomatic infection begins with about 3 days to 2 weeks following the exposure. Malaise, fever, vulvar pain and painful reactive inguinal lymphadenopathy are usually the first to occur. Shortly afterwards the first multiple small vesicles begin to appear on the vulva or vaginal and perianal mucosa [76]. The vesicles quickly turn into pustules, and due to the maceration in the moist environment of the vagina, these are replaced by numerous painful ulcers with yellowish-white erythematous base, which can be accompanied by intermittent bleeding and vaginal discharge. The ulcerative phase typically lasts about 10 days. Then the ulcers crust over and begin to heal, leaving no scars. In rare cases, herpetic infection can become chronic and chronic hypertrophic herpetic vulvovaginitis may clinically resemble a neoplasm (or in fact harbour an invasive squamous cell carcinoma) [65].

The microscopic appearance is usually evaluated in cytological smears or biopsies from the base or edges of a fresh ulcer (Tzanck preparation), keeping in mind that in a tissue section the characteristic changes are more commonly present at the edge of the ulcer [22]. The characteristic findings include vesicles involving the entire thickness of the epithelium, with infected cells showing typical bi- or multinucle-

ation and "ground-glass" nuclei (or the subsequent eosinophilic or basophilic intranuclear inclusions, best identified in viable epithelial cells or at the interface between the ulcer and viable epithelium). With the progression of the infection, the vesicles are transformed into ulcers, which are characterized by the presence of a diffuse, full-thickness epithelial necrosis consisting of dead and degenerating epithelial cells. In cases when the edges of the ulcer and the changes at their interface are not readily identifiable, HSV-targeted immunostaining can be of great help in highlighting the infected cells. The dermal stroma underlying herpetic ulcers may show a variable degree of inflammatory infiltrate, which may contain numerous neutrophils. It is also possible to use HSV-targeted in situ hybridization when in need of a diagnostic confirmation.

Although the histopathology of herpetic genital lesions is well described, in clinical settings the diagnosis usually does not require verification by a pathologist and is made based on the typical clinical presentation. Following the primary infection recurrent episodes (or a secondary infection) are fairly common and usually occur with the highest frequency during the first year after the initial infection.

9.2.4.2 Cytomegalovirus

In a healthy immunocompetent host, cytomegalovirus (CMV) infection is usually asymptomatic. If the infection does become clinically apparent, it is most commonly in the form of mononucleosis syndrome, and its association with vulvovaginitis (or cervicitis) is rare [79]. Cytomegalovirus infection, similarly to genital herpes, begins with the eruption of multiple small vesicles which turn into vaginal ulcers, which makes it easily confused with HSV infection, and the frequency of CMV vulvovaginitis is probably underestimated [79]. In HIV-positive patients, the ulcers can also involve the cervix and vulva, and in severe cases of immunosuppression, they can take on an aphthous appearance, often be very deep and even progress to fistulas.

Microscopically, vaginal swabs from the freshly unroofed vesicles show changes involving the entire epithelium. The infected epithelial cells characteristically display one enlarged nucleus, intracytoplasmic inclusions, and, similarly to HSV, intranuclear inclusions can also be observed. The nucleus has been described to have an "owl's eye" appearance due to a peripheral clearing of the chromatin [22]. The diagnosis can be further confirmed by immunohistochemical staining or PCR, especially in cases when the differentiation between HSV and CMV is problematic.

9.2.4.3 Epstein-Barr Virus

The Epstein-Barr virus is a rare cause of painful, ulcerative genital disease, found predominantly in teenage or young adult women [65]. Apart from genital ulcers, other symptoms of the disease include the typical features of mononucleosis (malaise, fever, sore throat) and lymphadenopathy, which may be distant from the site of the ulcers. The onset of genital ulcers may even precede the manifestation of mononucleosis and be the first sign of an active EBV infection. As the vulvar and vaginal pathology tends to be nonspecific, the final diagnosis can be confirmed serologically (by increased titres of antibodies against the viral capsid antigen, early antigen or nuclear antigen) or with the use of PCR. Microscopy of the ulcerated lesions shows infiltration with acute and mononuclear inflammatory cells, while the intact non-ulcerated lesions may display only mild, superficial chronic inflammatory perivascular infiltrate [76].

9.2.4.4 HIV

The prevalence of women among the HIV-infected population has been steadily increasing since the 1980s, when women made up 8% of all AIDS cases reported in the United States, to the 25% reported by the late 1990s. In 2000, women represented about 40% of the infected population worldwide, with almost 12 million female patients with HIV [80].

In women, the genital tract represents the most common acquisition and transmission site of the virus, as well as a reservoir for HIV once the infection has been contracted [81]. Although HIV/AIDS shows no gross or microscopic changes specific to the vagina, recently it has been discussed that in HIV-positive women, the genital tract may become a site of chronic inflammation causing a disruption of the epithelial barrier [82].

The significance of HIV when discussing vaginal infections lies in the synergistic relationship between HIV and other sexually transmitted diseases, as the presence of an STD is considered to increase the risk of both acquiring and transmitting HIV [80, 83]. The factors implicated in contracting the human immunodeficiency virus infection include the inflammation associated with STDs (which may increase the local concentration of immune cells in the vulvovaginal region, allowing for them to be targeted by HIV) and the presence of ulcers in some of the STDs, with the ulcers serving as a gateway for the virus [84].

9.2.5 Genital Manifestations of Other STDs

Sexually transmitted infections comprise a wide range of causative agents and clinical presentations, usually sharing a common feature of involving various parts of the lower genital tract with systemic symptoms and involvement. Many of the infections have been historically well-known and their pathogenesis, manifestation and symptoms well-established by the standards of modern medicine. For the purposes of this chapter, only the vagina-specific morphology and clinical manifestation will be discussed.

9.2.5.1 Genital Ulcer Disease

Syphilis

Syphilis is an ulcerative disease caused by the spirochete *Treponema pallidum*, which can cause significant complications in an untreated individual and has been associated with an increased risk of the acquisition and transmission of the HIV infection [75, 77]. In 2012, the estimated prevalence of syphilis was 18 million cases worldwide, with an estimated incidence of 5.6 million new cases in men and women ages 15–49 globally, making syphilis the least common of the four main curable STDs, the others being chlamydia, gonorrhoea and trichomoniasis [85].

The primary lesion of syphilis is the syphilitic chancre, which is most commonly seen on the skin of the vulva and perianal regions although the vaginal, cervical or oropharyngeal mucosa may also be affected. The presentation of the typically non-painful chancre is followed by a regional lymphadenopathy, fever and malaise, and if left untreated, the rapid systemic dissemination of the pathogen may progress to the secondary (characterized by mucocutaneous rash and papules—condylomata lata) and tertiary stage (leading to the formation of granulomatous lesions—gummas) of the disease [78].

The gross pathology of the chancre is characterized by an indurated ulcer with a typical "punched-out" appearance. Histologically, there is a marked dermal infiltrate of lymphocytes, macrophages and neutrophils, with a perivascular plasmacellular infiltrate accompanied by endothelial swelling and proliferation (also called plasma cell endarteritis) [65, 76]. The edges of the ulcers often show pseudoepitheliomatous epidermal thickening. For the demonstration of the organism within the lesion, silver stains (such as Warthin-Starry or Steiner stain) have traditionally been used, revealing the spirochetes in their typical perivascular distribution. Another method of detection is the dark field examination of secretions expressed from the lesions; however, the rather low sensitivity and often high background of these methods are not ideal, and in doubtful cases the application of immunohistochemical stains is preferable [76, 78].

Condylomata lata, the lesions of secondary syphilis, are typically found on various mucocutaneous surfaces, which in the genital tract may include the vagina although the involvement of the vulva is much more common. The lesions are characterized by a broad morphology with the macroscopic appearance of papules, pustules, macules and hyperkeratotic lesions. Histologically, the early changes are usually observed in the form of perivascular dermatitis with numerous plasma cells in the infiltrate, without any significant changes in the overlying epithelium. With the progression of the disease, the lesions can take on a lichenoid histomorphology with a psoriasiform epidermal hyperplasia, accompanied by a dense, band-like inflammatory infiltrate at the dermoepidermal junction, consisting predominantly of plasma cells, lymphocytes and macrophages. It is not uncommon for this infiltrate to spread and involve the deep vascular plexus. If the lesions are rich in spirochetes (which may be observed as slender, "left-handed" spirals with a length of 6–16 μm), the epidermis may show psoriasiform spongiform pustules containing neutrophils either in the epidermis or in the superficial crusts covering these lesions. The involved vessels may display variable endothelial swelling. The inflammatory infiltrate in late-stage lesions is often of a more granulomatous character, with the presence of epithelioid granulomas [22].

Tertiary lesions occurring in the genital tract are extremely rare, and, if present, they are characterized by gummas with central area of necrosis, surrounded by fibrous lymphohistiocytic infiltrate with numerous plasma cells [76].

Chancroid

Chancroid is a rare infection caused by *Haemophilus ducreyi*, a Gram-negative bacillus which is most prevalent in the tropical and subtropical areas. The typical clinical presentation is a combination of painful genital ulcers and tender suppurative inguinal lymphadenopathy. The gross pathology is characterized by single or multiple erythematous papules, which change into pustules, and following the rupture of the pustule's cover, a shallow ulcer is formed, releasing purulent exudate and revealing a friable, erythematous base with ragged undermined edges [78]. The individual lesions are usually small, measuring approximately 1–2 mm in diameter, and once the lesions become ulcerative, they may form larger confluent areas of up to 3 cm in diameter [12].

Biopsies are not usually required for the diagnosis, which (especially in the endemic regions of the disease) is often made based on the clinical symptoms alone. However, evaluation of the histopathology may be needed when other ulcerative conditions (such as herpes and syphilis) need to be excluded. The microscopic appearance of the chancroid ulcers shows a characteristic three-zone distribution: (1) a superficial zone with neutrophilic infiltrate, fibrin and erythrocytes, (2) a middle zone with vascular changes and a band of granulation tissue and (3) a deep zone with marked lymphoplasmacellular infiltrate [65, 76].

Lymphogranuloma Venereum

Lymphogranuloma venereum (LGV) is caused by the L1, L2 and L3 serotypes of the obligatory intracellular microorganism *Chlamydia trachomatis*. Traditionally, LGV was a disease endemic to tropical and subtropical areas, but in recent years a number of cases have been reported in Europe, North America and Australia [86]. LGV is an ulcerative disease where the first clinical manifestation is situated in the inoculation site, which is mostly the vulva, but an involvement of the vagina is also possible.

Similarly to syphilis, LGV infection progresses in three stages. The first stage occurs at the site of inoculation, beginning with the development of painless, small and shallow genital ulcers or papules [78]. In the vagina, these are most commonly found on the posterior vaginal wall and may be accompanied by a mucopurulent vaginal discharge. The accompanying infiltrate consists of mixed chronic inflammatory cells, with numerous plasma cells, lymphocytes and histiocytes including giant cells [65]. Granulomas can be present. The ulcers are self-resolving and heal without any residual scarring.

The second stage involves the regional lymph nodes and presents as painful lymphadenopathy. In men, inguinal adenopathy is the most common, while only about 20% of infected women present with lymphadenopathy at this site, and the most predominant lymphadenopathy is intra-abdominal or retroperitoneal (when the primary lesion is located on the posterior wall of the vagina), causing a clinically symptomatic anorectal syndrome [87]. The affected lymph nodes are usually matted in clusters (buboes) and frequently rupture spontaneously with the formation of fistulas and sinus tracts. If a biopsy of these lymph nodes is taken, it may reveal a characteristic stellate (or serpiginous) area of necrotizing inflammation, which may be surrounded by areas of acute inflammation with abscess formation, chronic inflammation or a granulomatous inflammation ("suppurating granulomas") [76].

The tertiary state of LGV is a result of untreated infection and comprises local complications due to extensive necrosis and scarring of the affected lymph nodes. The damage to the lymphatic drainage can lead to a local lymphoedema or even in extreme cases elephantiasis of the genitalia [62]. The reparatory process often leads to a fibrotic scarring of the vagina and rectum, resulting in genito-anorectal syndrome, chronic proctitis, rectal stenosis, scarring of the vulva and the formation of strictures and fistulae [87].

Due to the largely nonspecific histopathological findings, the diagnosis can be supported by immunohistochemical staining and is made in correlation with serology (complement fixation tests) and culture.

Granuloma Inguinale

Granuloma inguinale is an ulcerative genital disease otherwise known as donovanosis, caused by the intracellular Gram-negative bacteria *Klebsiella granulomatis*, previously known as *Calymmatobacterium granulomatis*. The primary lesions may be found in the vulva, vagina or cervix following the inoculation through sexual contact or faecal contamination [65].

Macroscopically, the lesions are made up of painless erythematous papules, nodules or progressive ulcers (the most common, ulcerovegetative form of the disease) [62]. The ulcers eventually merge together to form larger areas of hypertrophic, "beefy red" granulation-like tissue with rolled edges, which is highly vascular and frequently bleeds upon contact. In some cases the ulcers persist for a long time (months to years) and may resemble a squamous cell carcinoma in their appearance. Associated inguinal lymphadenopathy is not common with granuloma inguinale (unlike LGV), but it may be mimicked by the formation of subcutaneous, ulcerating abscesses termed pseudobuboes [78].

Smears or biopsy samples taken from the ulcerated lesions consist mostly of granulation tissue, rich in mixed inflammatory infiltrate consisting of neutrophils, macrophages, plasma cells and lymphocytes. The chronic inflammatory infiltrate may extend into the dermis, frequently associated with endarteritis of the dermal vessels. The cytoplasm of some of the macrophages contains the pathognomonic vacuoles with ingested coccoid to bacillary organisms displaying characteristic surrounding halos, called Donovan bodies. In some cases, these may also be observed extracellularly. The Donovan bodies are key to the microscopic diagnosis and can be best visualized on a Giemsa or Warthin-Starry (the appearance of small safety pins) stained slide, which is prepared by pressing the biopsy tissue from the edge of the ulcer between two slides and then staining the imprint. The ulcerated surface is often covered by a fibrinous exudate, with multiple necroses and microabscesses within the epidermis [12, 62, 65, 76]. If left untreated, the natural course of the disease is slow and progressive, and healing of the (often extensive) ulcerations leads to the formation of abundant, disfiguring fibrous tissue which can eventually result in genital mutilation.

9.2.5.2 Discharge-Causing Diseases

Gonorrhoea

Gonorrhoea, a disease caused by the organism *Neisseria gonorrhoeae*, is the second most commonly reported bacterial STD in the United States, with a total of 350,062 cases reported in the United States in 2014 and a national gonorrhoea rate of 110.7 cases per 100,000 population [77]. Literary data estimated the global prevalence of gonorrhoea in 2012 to be 27 million cases, with an estimated incidence of 78 million cases [85].

In the female genital tract, gonorrhoea is associated predominantly with infectious cervicitis and as such plays an important role in the development of pelvic inflammatory disease and also has been associated with various negative pregnancy outcomes [75]. The mucopurulent discharge, one of the main clinical symptoms of gonorrhoeal cervicitis, can sometimes be suggestive of a vaginal infection, but a simple colposcopy exam is usually sufficient to rule out this entity.

Chlamydia Trachomatis

Chlamydia is the most frequently reported bacterial sexual transmitted disease, with the estimated overall worldwide prevalence of 128 million cases and incidence of 131 million new cases a year [85]. In the United States alone, there was a

total of 1,441,789 cases of chlamydial infection reported to the CDC in 2014, corresponding to a rate of 456.1 cases per 100,000 population [77]. The significant morbidity associated with this curable STD includes pelvic inflammatory disease, chronic pelvic pain, tubal infertility and increased risk of ectopic pregnancy [75].

The infection is most common in the adolescent population and often clinically asymptomatic. It is a frequent cause of cervicitis, causing a mucopurulent discharge which not unlike in the case of gonorrhoea may mimic bacterial or aerobic vaginitis. On closer inspection however, mucopurulent cervicitis is easily distinguishable from such entities. In some cases, the inflammation may show chronic inflammatory infiltrate, sometimes even leading to follicular cervicitis with multiple subepithelial and periglandular lymphoid follicles in the endocervical mucosa, often with germinal centres [65]. The causative *Chlamydia* microorganisms can be confirmed by immunohistochemical staining. If a biopsy specimen is not available, chlamydial infection can also be observed in a cervical smear. The typical (although not always present) signs include cytoplasmic vacuolization, squamous and glandular cells with a ragged cytoplasmic border (so-called moth-eaten appearance) and a coccal-like background with a few scattered neutrophils. In the case of follicular cervicitis, occasional streaks of lymphocytes and their immature forms may be distinguishable [62].

9.2.6 Parasitic Infections

Parasitic vaginitis has traditionally been a rare entity in developed countries, but the incidence is likely to increase as the global travel and migration increases as well. In the endemic regions of mostly tropical and subtropical climate of Africa, Central America, Middle East and Asia, these infections are encountered much more frequently and constitute an important source of reproductive morbidity in women.

9.2.6.1 Schistosomiasis

Schistosomiasis (or bilharzia) is an intravascular infection caused by the freshwater trematode worms *Schistosoma*, which are endemic especially to the tropical and subtropical regions of Africa, Asia and the Middle East. The transmission occurs when a person is in contact with freshwater contaminated by faeces or urine containing the parasite eggs, which first infect a specific freshwater snail (in case of *S. haematobium* the *Bulinus* snail) serving as an intermediate host from which the infection can be transmitted to humans [88]. Most commonly, female genital schistosomiasis (FGS) is caused by an infection with *S. haematobium* (also termed urinary schistosomiasis, or more recently urogenital schistosomiasis), but there are also reports of genital affliction with *S. mansoni* and *S. japonicum* [89]. The deposition of schistosomiasis eggs follows their transmission into the genital tract, which occurs via blood vessel anastomoses in the pelvic organs. It is assumed that in cases of pure *S. haematobium* genital infection (without the involvement of the urinary tract), the transmission probably occurred due to individual blood vessel patterns, blood flow and the localization of worms.

The lower female genital tract is a common site for the deposition of *Schistosoma haematobium* ova, and it is estimated that probably millions of women may suffer from an undiagnosed genital schistosomiasis. The reported prevalence of FGS in its endemic areas ranges from 33 to 75% [89]. The infection is a significant cause for morbidity, and it has been associated with infertility, preterm delivery, increased risk of extrauterine pregnancy, menstrual disorders and lower abdominal or back pain [90, 91].

The clinical presentation of genital schistosomiasis may be very mild or completely asymptomatic. The most commonly recorded subjective complaints are of a malodorous, bloody or yellow vaginal discharge, dysuria, low abdominal pain, dyspareunia and postcoital bleeding [90]. Other symptoms associated with FGS also include genital itching, stress incontinence and pollakisuria [92]. A serious and debilitating complication of chronic vaginal schistosomiasis is the formation of rectovaginal and vesicovaginal fistulas, often requiring surgical intervention [93].

Colposcopic examination reveals either the characteristic "sandy patches", which are typically located predominantly on the cervix, or polypoid/papillomatous tumour-like prominences and papulae with irregular surface, which are more common to the vaginal walls and vulva [94]. Sandy patches are described as slightly elevated lesions with a characteristic rough, sand-like surface which is gritty on section. The correlating histologic image shows marked areas of fibrosis with disintegrated eggs and only a minimal inflammatory infiltration. On the other hand, the polypoid or papillomatous lesions consist of large masses of mostly viable eggs, with a dense surrounding inflammatory reaction rich in eosinophils. Both sandy patches and polypoid/papillomatous lesions may show epithelial hyperplasia. Erosions and superficial ulcerations of the vagina and vulva have also been described. The infection is characterized by the deposition of eggs, either inside the epithelial layer or inside the connective tissue stroma. The eggs themselves are usually easy to identify due to their characteristic size, shape and a lateral or terminal spine, especially if there is a clinically expressed suspicion of this diagnosis [88]. Careful examination may demonstrate either viable eggs (with mature miracidia containing intact germinal cells) or calcified, non-viable ova. The surrounding tissue reaction ranges from an abundant granulation tissue with numerous newly formed blood vessels and immature fibroblasts to areas of fibrosis. Fibrosis is ultimately considered to be the end-stage pathology in schistosomiasis.

Until recently, the gold standard for diagnosis was considered to be the crushed biopsy of genital tissue (quantitative compressed biopsy technique, QCBT). The tissue is crushed between two glass slides, together with a drop of 0.5% tryptan blue in physiological saline (aiding in the microscopic differentiation between dead and viable eggs) and examined microscopically [90, 93]. However, ethical concerns have been raised about the performance of a diagnostic biopsy, seeing as the procedure is invasive, associated with bleeding and may lead to blood exposure during sexual intercourse between the female and her partner, raising the risk of HIV acquisition and transmission [95]. Also, the focal localization of the eggs means that they might be missed in a crushed biopsy. After the 2010 FGS consensus meeting in Copenhagen, it was established that in endemic areas the presence of at least one of the three defined visual clinical findings is sufficient to make the diagnosis. These findings are (1) aceto-negative single or clustered grains, (2) homogenous yellowish sandy patches and (3) rubbery tubercles or papules [96]. Wet smears and Pap smears may also help in identifying the parasite eggs, but with a reported value of 15%, their sensitivity is rather low [89].

9.2.6.2 Enterobiasis

Enterobiasis is an infection caused by the nematode *Enterobius vermicularis*, also known as pinworm, threadworm or seat-worm. It is the most common helminthic infection in humans, with a prevalence of about 209 million people infected worldwide [97].

Enterobius vermicularis (EV) is considered as a mainly intestinal parasite, living predominantly in the caecum and colon. The gravid females of the parasite migrate to the perianal region at night, where they emerge on the perianal and perineal skin and deposit their eggs [98].

Extraintestinal enterobiasis is a rare presentation of the infection caused by migration of the pinworms into other anatomical locations, most commonly to the female genital tract [99]. Both the upper and lower genital tract may be affected, with a suggested ascending course of pinworm migration which can even reach past the fallopian tubes and ovaries into the pelvic peritoneum or even infect the human embryo [100]. In some cases, EV was identified as the cause of extensive pelvic masses, pelvic pain mimicking endometriosis, pelvic inflammatory disease (necessitating hysterectomy with bilateral salpingo-oophorectomy) and ovarian cysts [97]. The most serious gynaecological complications of invasive female genital tract enterobiasis include bacterial co-infection, infertility, tuboovarian abscess formation, granulomata of the vulva, uterus and ovaries and generalized peritonitis [99, 100].

The proposed mechanism of female genital tract infection is a direct migration of the parasites from the anus and perianal region into the vagina. It has also been suggested that the vagina may serve as a potential reservoir for EV [98].

A variety of clinical symptoms have been reported, ranging from vaginal discharge, vulvar and vaginal itching and postcoital spotting to a severe, distressing nocturnal perineal or vaginal pain [97, 99, 101]. However, the majority of the cases represented an incidental finding in asymptomatic females (>70%).

The diagnosis of a classical *Enterobius vermicularis* infection is based predominantly on the clinical symptoms, typical patient history and the demonstration of the eggs, usually on a piece of a tape that is applied over the anus and left in place over night. In case of genital enterobiasis, live pinworms can sometimes be spotted in either the vaginal introitus or collected from vaginal swabs, usually from the anterior or posterior fornix [97, 102]. Tissue biopsies are not routinely performed for this diagnosis, but the presence of the nematode may be an incidental finding especially in cases of pelvic involvement mimicking malignancy.

The characteristic smear finding is of variable amounts of EV eggs. The inflammation may be mild or severe and is an important sign that the *Enterobius* parasite actually originated in the genital tract rather than contaminated the slide from its usual perianal distribution. The inflammatory infiltrate usually contains numerous neutrophils and cellular debris, and in some cases there are also eosinophils and macrophages present. The eggs have a typical appearance of small, ovoid, flattened objects resembling pumpkin seeds in shape, with dimensions between 20 and 60 μm [103]. The shell of these eggs is characteristically thick, double-contoured and birefringent. Inside the eggs there may be visible coarsely granular embryos or curved larvae in different stages of delivery (entirely inside the egg, partially expelled or completely delivered) [99]. The background may also frequently show reactive and reparative columnar cells, sometimes almost completely obscured by the inflammatory infiltrate. The differential diagnosis includes mainly other parasitic infections (especially *Trichuris trichiura*, *Strongyloides stercoralis*, *S. haematobium* and *Entamoeba histolytica*), but also contaminating materials such as pollen (brown, oval structures measuring approximately 10 × 2 μm, with refractile smooth walls, an absence of nuclei and internal structures, sometimes forming chains) [103, 104].

9.2.6.3 Other Rare Parasitic Vaginitides

Vaginal amoebiasis is a rarer presentation of *Entamoeba histolytica* infection. Classic amoebiasis affects the large intestine and leads to amoebic dysentery, colitis and development of liver abscesses [105]. *E. histolytica* has an infective cyst stage and a pathogenic, motile trophozoite stage. The trophozoites may form larger aggregates and behave as microemboli, being carried via the bloodstream to other organs

(particularly portal circulation), which is considered to be one of the possible ways of extraintestinal spread. However, there are cases of female genital amoebiasis with no documented intestinal infection [106].

The main clinical findings are represented by ulcerative lesions with indurated base located on the vulva, vagina or cervix, the appearance of which may often mimic carcinoma (which in some cases was found together with the amoebiasis-caused ulcer) [105]. The ulcers may be covered by a fibrinopurulent exudate resembling "anchovy sauce", with numerous microscopic trophozoites [22]. Neglected cases of uncontrolled infection have been demonstrated to progress in a locally devastating manner, leading to necrotizing vulvitis requiring a surgical intervention or even a radical vulvectomy [105].

The microscopic diagnosis is most commonly done in cervical or cervicovaginal smear specimens or in a biopsy of the ulcerated lesion. The cytological appearance of the parasite is that of round or ovoid shapes with a diameter of 15–60 μm, with a basophilic staining and clearly defined ectoplasm and endoplasm. The endoplasm has a finely granular structure and shows one of the most typical characteristics of *E. histolytica*—the parasite frequently ingests erythrocytes, which can be visible as orange or pink spheres within the phagocytic vacuoles and greatly aid in establishing the diagnosis of amoebiasis [107]. The ectoplasm on the other hand is less basophilic and more homogenous and often shows a typical "helmet-like" placement covering only about half the surface of the trophozoite, taking on a crescent shape. In some cases the trophozoites might not be well preserved on the slide, and the ectoplasm becomes less distinguishable, giving the appearance of a clear halo around the endoplasm. The nuclei are often placed eccentrically, with a characteristic, central small karyosome, delicate peripheral chromatin and a single unidirected pseudopod [108]. The background of the smears has been described as "dirty", given by the presence of numerous leucocytes, red blood cells, histiocytes, bacteria (frequently with *Trichomonas vaginalis*) and intermixed cell detritus [107].

In tissue sections, the amoebic penetration through the vaginal mucosa causes extensive cell necrosis. The very commonly occurring secondary bacterial infection leads to frequently observed purulent sloughing of the mucosa and the dense inflammatory infiltrate in the submucosa [106].

9.3 Other Benign Disorders of the Vagina

9.3.1 Malacoplakia

The term "malacoplakia"is derived from the Greek "malakos" (soft) and "plakos" (plaque), first described in 1901 by von Hansemann. Malacoplakia is a rare granulomatous disease caused by impaired macrophage response, most commonly involving the urinary tract. The etiology and pathogenesis of malacoplakia is still not fully understood, but it is proposed that it is associated with immunosuppression, infection and systemic illnesses. An important role is played by some bacteria, such as *Escherichia coli*, *Proteus*, *Mycobacterium tuberculosis* and *Staphylococcus aureus*, but it is clear that other factors must contribute as well, since these infections are much more common than malacoplakia itself. Malacoplakia could therefore be the result of improperly functioning lysosomes, probably caused by a low level or deficit of cyclic guanosine monophosphate and/or β-glucuronidase (both essential to efficient lysosomal bactericidal activity), leading to the incomplete removal of bacteria and the persistence of bacterial residues within the phagolysosome [109].

9.3.1.1 Gross and Microscopic Features

In the vagina, malacoplakia typically forms yellow polypoid nodules arising from the vaginal mucosa, sometimes accompanied by a vaginal discharge [8]. They may also present as a mass lesion. Microscopically, the lesion is characterized by the accumulation of histiocytes with abundant granular to pale foamy cytoplasm (von Hansemann cells) (Fig. 9.6). There are also numerous interspersed plasma cells, lymphocytes and a variable numbers of intracellular and extracellular concentrically laminated basophilic masses (Michaelis-Gutmann bodies), scattered in a scant fibrous stroma, infiltrated with lymphoid cells. Michaelis-Gutmann bodies are supposed to arise from the mineralization of calcium and iron salts on residual microorganism glycolipids. They are pathognomonic of malacoplakia and their finding is fundamental for the diagnosis [109]. The

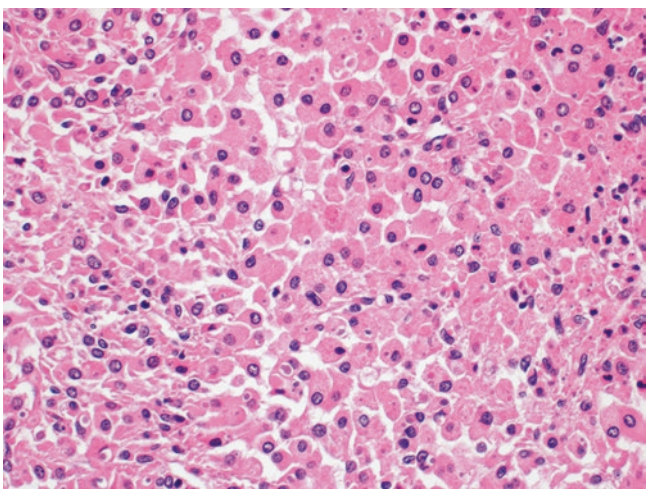

Fig. 9.6 Malacoplakia. The lesion is characterized by the accumulation of numerous histiocytes with abundant cytoplasm. Numerous amphophilic or basophilic laminated bodies (Michaelis-Gutmann bodies) can be seen

correct diagnosis may be supported by the finding of degenerating bacteria on tissue Gram stain, silver stain or by electron microscopy [8]. In a final "end-stage", malacoplakia may show significant scarring, making the aforementioned pathognomonic cells difficult to identify.

9.3.1.2 Differential Diagnosis

The differential diagnosis includes nonspecific granulomatous inflammation and haematopoietic neoplasms, with which malacoplakia may rarely coexist. As previously noted, the finding of Michaelis-Gutmann bodies establishes the diagnosis. Concurrent haematopoietic diseases can be excluded by careful analysis of the density, phenotype and distribution of the non-histiocytic populations.

9.3.2 Trauma and Iatrogenic Injury

9.3.2.1 Trauma

Vaginal lacerations can occur in association with an injury to the pelvic area (in particular in pelvic fractures), in penetrating injuries, and after vaginal delivery, especially with instrumental deliveries. An episiotomy, a surgical cut of the vagina and perineum, may prevent serious tears during childbirth, but on the other hand, an episiotomy guarantees perineal trauma and sutures. Patients with vaginal lacerations present with abnormal vaginal discharge or intermenstrual bleeding.

Tampon use may also cause ulcerations of the vaginal mucosa, and in rare cases toxic shock syndrome has been described. Tampon ulcer is typically a single ulcer with an irregular border of granulation tissue, mostly localized in one of the vaginal fornices [110]. Microscopically, the ulcers may contain fibrillar foreign bodies within the exudate, and the ulcers heal spontaneously within 2–3 months after ceasing tampon usage (Figs. 9.7 and 9.8) [110]. The pathogenic mechanism for the association of tampons with toxic shock syndrome is not well understood. Menstrual toxic shock syndrome is thought to be associated with colonization by toxic shock syndrome toxin-1 producing *Staphylococcus aureus* in women with insufficient antibody titres [111]. One of the proposed mechanisms is that tampon use further enables the production of toxic shock syndrome toxin-1 by exposing the vagina to more oxygen [112].

9.3.2.2 Fistula

Vesicovaginal and ureterovaginal fistulas are a rare complication of female pelvic surgery, most commonly the result of gynaecological surgery. Other causes include radiotherapy, injury during the healing process or severe pelvic pathology (such as pelvic tumour, trauma, congenital anomalies, foreign body and abscess). In developing countries genitourinary fistulas are most commonly related to childbirth [113].

Fistulas are usually painless and result in the leakage of urine from the vagina, which might be either intermittent or, more characteristically, continuous. They can cause vulvar irritation or more serious recurrent infections or pyelonephritis which can be the cause of renal insufficiency. Microscopically, little or no epithelial lining, variable amounts of granulation tissue, fibrosis and chronic inflammation can be seen. Infrequently, vaginal calculi which originate from the deposition of urinary salts in the vagina may be present.

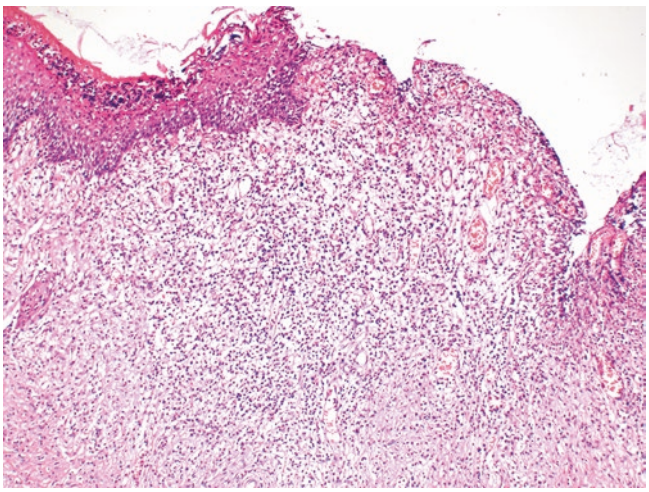

Fig. 9.7 Chronic tampon ulcer. The epidermis at the edge of the ulcer is irritated, with numerous mixed inflammatory cells. Granulation tissue is apparent in the area of ulceration, with numerous vessels and pronounced inflammation

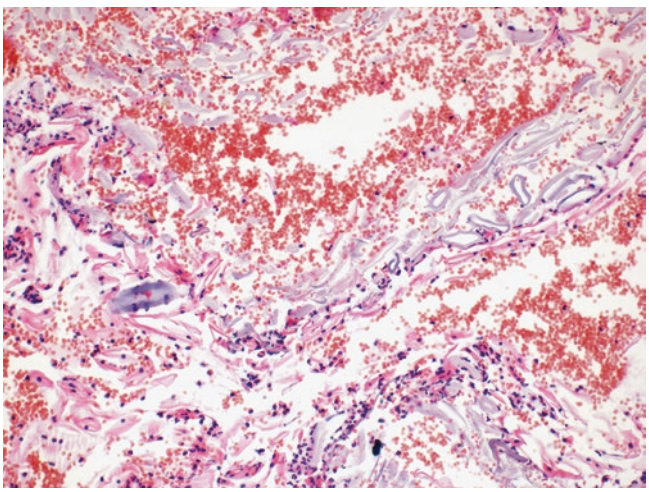

Fig. 9.8 Foreign (tampon) material. The fragments of tampon fibres intermingled with squamous cells, leucocytes and erythrocytes

9.3.2.3 Radiation

The vaginal alterations after radiotherapy may be divided into acute or chronic postradiotherapy reaction. The acute reaction occurs during or immediately after radiotherapy, and acute changes may include mucosal inflammation, hyperaemia, epithelial denudation leading to ulceration and

endothelial injury causing small-vessel thrombosis, oedema and smooth muscle necrosis [114]. The chronic postradiotherapy changes largely follow the general principles of chronic treatment complications and occur later than 3 months post radiotherapy. These reactions include changes in the microvasculature, with the loss of capillaries and impaired microcirculation, and changes in the vaginal mucosa caused by increased collagen production in the submucosal fibromuscular connective tissue. This leads to secondary atrophic changes of the vaginal mucosa, obliteration of the muscle and vasculature resulting in hypoxia, tissue atrophy and fibrosis with a shortening and stenosis of the vagina [114]. Eventually, ulceration, necrosis and fistulae can develop. Pathological dilation of capillaries also results in telangiectasias, which are prone to bleeding. In addition to these more general changes, treatment-related loss of ovarian function and consequent hormonal insufficiencies can augment the mucosal alterations.

Microscopically, atrophic mucosa with thinned epithelium may be seen, along with fibrosis, vascular changes with obliteration and thrombosis. The dilation of small blood vessels lined with plump endothelial cells containing large nuclei with vesicular chromatin may also be observed. There may also be variable infiltrates of plasma cells, granulation tissue and bizarre stromal cells with pleomorphic, hyperchromatic nuclei which may be scattered within the stroma (Fig. 9.9).

9.3.2.4 Pelvic Organ Prolapse

Pelvic organ prolapse is defined as the descent of one or more of the anterior vaginal wall, the posterior vaginal wall, the uterus or the apex of the vagina [115]. The prolapse is principally associated with vaginal delivery, which may lead to pelvic floor muscle and connective tissue injury, but the cause of prolapse is multifactorial. Hysterectomy, pelvic surgery and conditions associated with increased intra-abdominal pressure (including obesity, chronic cough, constipation and repeated heavy lifting) also contribute to prolapse. Its prevalence increases with age, and it may occur in up to 50% of parous women.

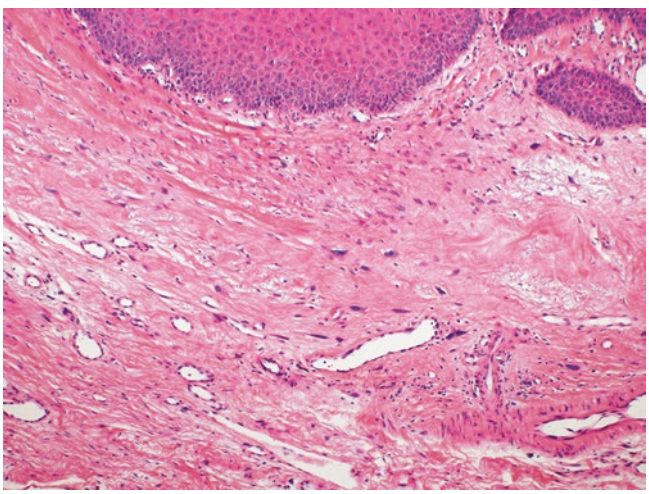

Fig. 9.9 Postradiotherapy changes. There is a fibrosis of lamina propria with increased amount of elastic fibres, dilatation of capillaries and mild chronic inflammatory infiltrate. Stromal cells with hyperchromatic atypical nuclei are scattered within the stroma

The prolapse is either asymptomatic or presents with various symptoms including vaginal bulge, pelvic pressure and incontinence. Microscopically, vaginal mucosa presents variable degrees of acanthosis, hyperkeratosis or parakeratosis; sometimes erosions or reparative changes can be seen. Treatment options include observation, surgery and the use of vaginal pessaries. The surgical options are reconstructive pelvic surgery with or without mesh augmentation and obliterative surgery [116].

9.3.3 Emphysematous Vaginitis

Emphysematous vaginitis is a rare condition, characterized by the presence of multiple, discrete, gas-filled cystic cavities in the vaginal mucosa and on the exocervix. It is a benign, self-limited disease with a benign clinical course. Its etiology is not completely understood, but it is proposed that it could be an unusual manifestation of a common vaginal infection in immunocompromised patients [117]. Although a number of microorganisms have been studied, a confirmed relationship with emphysematous vaginitis has only been found for *Trichomonas vaginalis* and *Gardnerella vaginalis* [118].

The lesions present as variably sized nodules (gas-filled bubbles), most commonly in the upper two thirds of the vagina and/or on the cervix, on occasion producing crepitus or a "popping sound" which relieves the pressure sensation. Chemical analyses of the gaseous content show a wide variety of gases, with high proportions of nitrogen and oxygen and smaller proportions of carbon dioxide, sulphur dioxide and argon [118]. The patients mostly present with symptoms of pruritus and vaginal discharge, although some are aware of popping sounds during sexual intercourse. Microscopically, the lesion is characterized by variably sized cysts in the stroma, which may be empty or contain pink, hyaline-like material. The cysts are mainly located in the outermost portion of the lamina propria in the subepithelial space and are lined by either multinucleated giant cells, squamous cells or both and accompanied by minimal chronic inflammatory cell infiltrate (Fig. 9.10a, b) [8].

9.3.4 Desquamative Vaginitis

Desquamative inflammatory vaginitis is a rare form of chronic vaginitis, characterized by yellow discharge, vaginal irritation and dyspareunia. The vaginal walls show signs of inflammation with increased erythema and petechiae, mainly

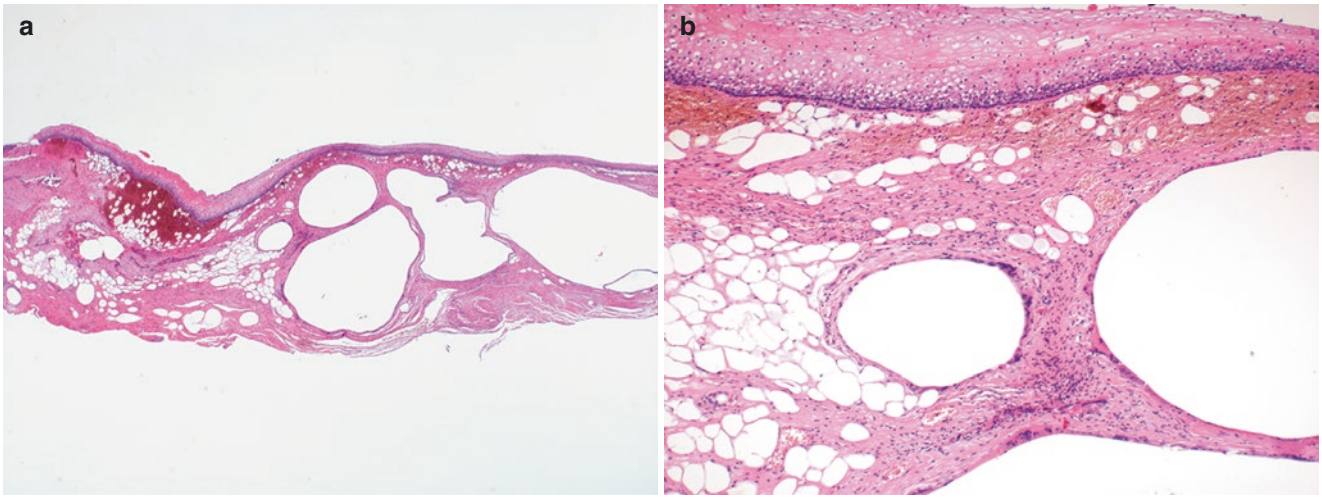

Fig. 9.10 Emphysematous vaginitis. Low-power view showing numerous variable-sized empty spaces located in the vaginal wall (**a**). Some of the cysts are lined by multinucleated giant cells. There is a mild focal chronic inflammatory infiltration in the stroma (**b**)

in the upper half of the vagina. Occasionally, erythematous papules with a pale centre or pseudomembranes are seen [119]. Symptoms and signs are nonspecific, and the diagnosis of desquamative vaginitis follows the exclusion of a wide range of all other disorders causing erosion (such as pemphigus vulgaris, lichen planus and pemphigoid). Infectious forms of inflammatory vaginitis also need to be carefully ruled out. Microscopically, the affected vaginal mucosa shows only a nonspecific inflammatory reaction. The vaginal discharge is usually copious, purulent to haemorrhagic with a high proportion of parabasal cells and numerous neutrophils. The vaginal flora is abnormal with lower levels or a loss of lactobacilli and their replacement by other organisms (mainly Gram-positive cocci and/or *Escherichia coli*) but is frequently negative for infectious pathogens [120]. The vaginal pH is always elevated above 4.5 [119]. Desquamative vaginitis usually affects premenopausal and perimenopausal women, with normal serum estrogen levels.

The etiology of the disease remains unknown, although a number of different etiologies have been suggested to play a key role in the pathogenesis. These include, for example, a bacterial infection, but no single bacterial or viral agent has been identified by culture. Kallikrein-related peptidases (serine proteases which play a crucial role in skin desquamation) have also been considered in the pathogenesis [121]. Due to the overlap of some of the symptoms and signs with other immune-mediated vaginal diseases (such as lichen planus and pemphigus), and the favourable response to anti-inflammatory agents, there is a suggestion that the etiology could be immune mediated, but the serologic studies needed to confirm an immune basis of the disease have not been forthcoming [119]. Desquamative vaginitis is commonly treated with vaginal clindamycin and local vaginal corticosteroids, with clinical improvement in more than 86% of patients [119].

9.3.5 Vaginal Calculus

Vaginal calculi are rare and can be classified as primary or secondary, depending on the presence or absence of a foreign body nidus. Primary vaginal calculi are more common than secondary calculi and originate from the deposition of urinary salts in the vagina without an obvious nidus. They can be caused by various etiological factors, such as vesicovaginal and urethrovaginal fistulas, congenital anomalies of the genitourinary tract or pelvis radiotherapy, vaginal outlet obstruction (acquired or congenital) and neurogenic bladder [122].

Primary vaginal calculi are usually associated with an infection with urease-producing bacteria, changing the normally acidic pH of the vagina to alkaline and therefore predisposing the precipitation of triple phosphate (struvite) calculi [123]. Secondary vaginal calculi result from the crystallization of urinary constituents around a foreign body in the vagina. In exceptionally rare cases, a preexisting bladder calculus may travel into the vagina through the vesicovaginal septum and become a secondary vaginal calculus [123]. Vaginal calculus can act as a foreign body, and it can reach such dimensions that it obstructs the whole vagina, with the resulting pressure on other organs causing obstruction of the bowel or urinary tract.

9.3.6 Atrophic Vaginitis

Atrophic vaginitis is a form of vaginitis caused by estrogen deficiency. It occurs in postmenopausal women as a physiologic event or in premenopausal women where it is caused by iatrogenic or otherwise mediated decrease of estrogen levels (administration of anti-estrogen medication as a part of the treatment for breast cancer, endometriosis, leiomyoma or infertility; chemotherapy- or radiotherapy-induced ovarian

failure; premature ovarian failure; endocrine or immunologic disorders). Some women may develop atrophic vaginitis postpartum due to the loss of placental estrogen or while breastfeeding due to the antagonistic action of prolactin on estrogen production. Some medications, smoking, tampon usage and condoms may also cause or worsen vaginal dryness.

The atrophic mucosa is thin and dry, with a loss of glycogen and a lack of lactobacilli, thus leading to the increase of vaginal pH, followed by changes in the vaginal flora. Transudation through the vaginal epithelium is reduced. Due to these changes, the thin, atrophic vaginal mucosa is more susceptible to injuries and infection from pathogenic bacteria such as staphylococci, group B streptococci and *E. coli*. Simple atrophy can thus transform into atrophic vaginitis. The patients may be asymptomatic, or there may be symptoms of vaginal dryness, itching, irritation, mucosal bleeding, dyspareunia and sometimes watery discharge. The vaginal mucosa is macroscopically pale, shiny smooth with a loss of rugal folds and easily traumatized. Often, inflammation with patchy erythema and petechiae may be present. Microscopically, there is a reduction or a loss of the superficial and intermediate cell layers; the epithelium may be thinned to six to eight layers of parabasal cells that may also predominate in cytologic vaginal smears (Fig. 9.11). Sometimes the degenerative features of parabasal cells can mimic dysplasia, which has to be excluded. There may be small ulcerations with acute inflammation interspersed among regions of intact atrophic epithelium. The submucosa is infiltrated by variably dense infiltrates of mononuclear inflammatory cells. Both systemic and topical estrogen treatments are effective in the treatment for relieving the symptoms of atrophic vaginitis, but topical vaginal estrogen is preferred because of the low systemic absorption and reduced risk of adverse effects when compared with oral therapy. The response to estrogen therapy is usually good, with epithelial cell maturation and a return of premenopausal flora and pH levels. Non-hormonal moisturizers are a beneficial alternative for patients with few or minor symptoms and in patients at risk for estrogen-related neoplasia [124].

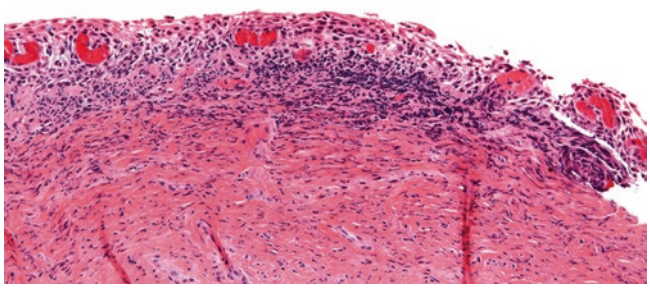

Fig. 9.11 Atrophic vaginitis

9.3.7 Vaginal Cysts

Cysts of the vagina are rare lesions which can be asymptomatic and represent incidental finding or can present as a vaginal or paravaginal mass [125]. Usually, the cysts are solitary lesions mostly less than 2.0 cm in diameter but can reach a size of up to 7.0 cm in diameter. Based on their histogenesis and the type of lining epithelium, the cysts can be classified as squamous inclusion, Müllerian, mesonephric (Gartner's duct), Bartholin gland and endometrioid. Other rare cysts in this area include the paravaginal/paraurethral cyst caused by an ectopic ureterocele and the paravaginal epidermoid cyst.

9.3.7.1 Squamous Inclusion Cyst

The squamous inclusion cyst is the most common vaginal cyst, which is usually secondary to episiotomy or surgical procedure. The size of these cysts varies from a few millimetres to several centimetres. Microscopically, the cyst is lined by stratified squamous epithelium. The cyst can be filled with keratin from desquamated squamous cells (Fig. 9.12).

9.3.7.2 Mesonephric (Gartner's Duct) Cyst

Mesonephric cyst is usually lateral or anterolateral and can be single or multiple. This cyst accounts for about 10% of vaginal cysts. It arises from a persistent, vestigial form of Wolffian ducts. The size varies from a few millimetres to several centimetres. Microscopically, the cyst is lined by bland-appearing cuboidal cells lacking cilia or intracellular mucin production (Fig. 9.13a, b). This feature is particularly helpful in the differential diagnosis against Müllerian cyst.

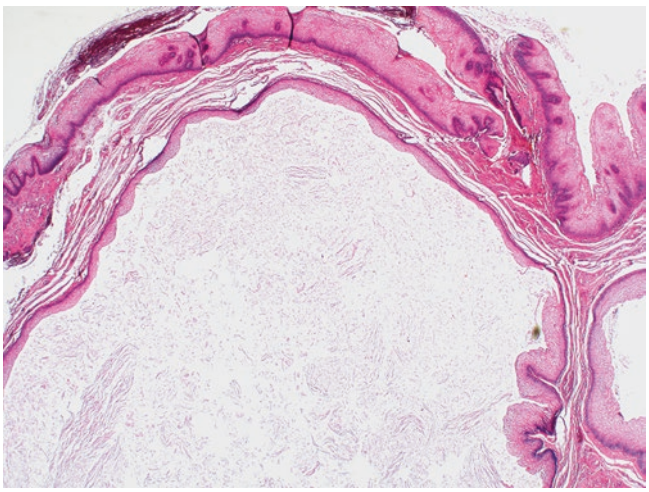

Fig. 9.12 Squamous inclusion cyst. The cyst is lined by a stratified squamous epithelium. Inside the cyst there is a keratin material

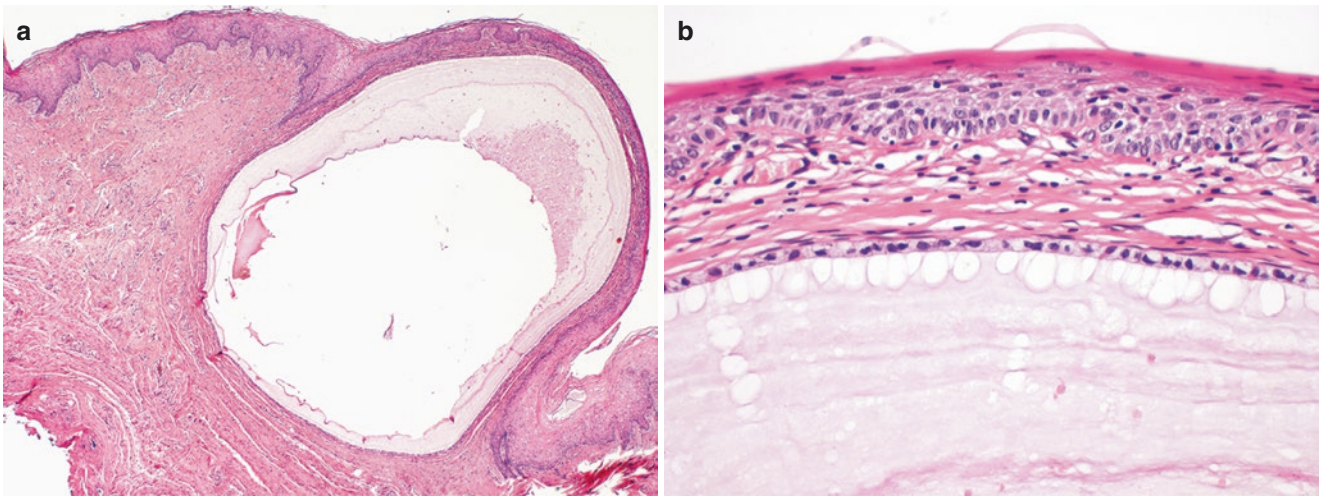

Fig. 9.13 Mesonephric (Gartner's duct) cyst. Unilocular cyst located directly beneath the superficial mucosal epithelium, containing eosinophilic material (**a**). The cyst is lined by a single row of cuboidal epithelium lacking cilia (**b**)

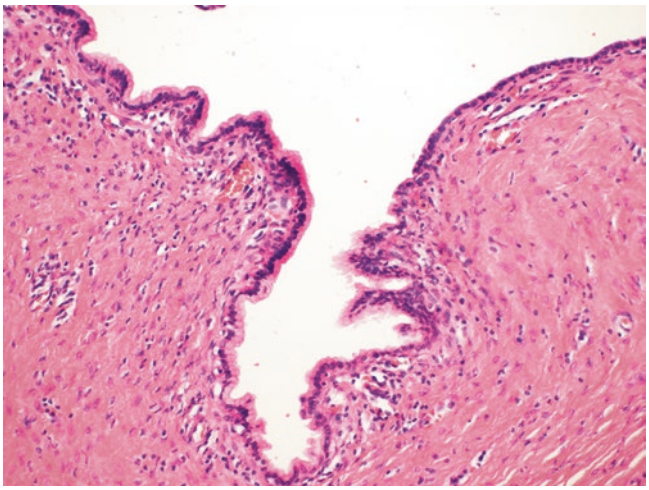

Fig. 9.14 Müllerian cyst. The cyst is lined by mucinous epithelium; however, any Müllerian type of epithelium can occur

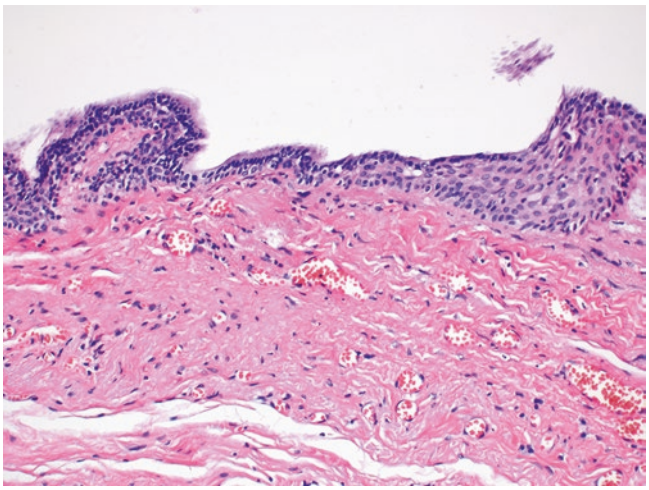

Fig. 9.15 Bartholin gland cyst. The cyst is partly lined by mucinous epithelium similar to the epithelium of normal Bartholin gland duct. On the right side metaplastic squamous epithelium is seen

9.3.7.3 Müllerian Cyst

Müllerian cysts usually present as small (up to 2 cm) midline cystic masses. Microscopically, the cysts may be lined by any type of Müllerian epithelium, including mucinous, ciliated tubal and endometrial (Fig. 9.14). Squamous metaplasia may occur.

9.3.7.4 Bartholin Gland Cyst

Bartholin gland cyst occurs in the distal part of vagina, near the opening of the Bartholin gland duct into the vestibule. This cyst is usually associated with occlusion of the duct, due to mucus retention, inflammation or trauma. Microscopically, the lining epithelium can be mucinous, squamous or transitional in type (Fig. 9.15). Commonly, all types of epithelium may be found within a single lesion. Inflammatory changes are not uncommon.

9.3.8 Vaginal Granulation Tissue

Granulation tissue occurring in the vagina is a common finding, especially after hysterectomy. It can, however, also be found in other settings such as mesh implants for uterine prolapse or can be associated with local trauma [126]. Grossly, granular or polypoid, single or multiple, reddish and sometimes haemorrhagic lesions are present. Clinically it may cause bleeding or discharge. Histologically, the lesion shows the typical features of nonspecific granulation tissue, which is highly vascular with pronounced inflammatory infiltrate including neutrophils, lymphocytes, plasma cells and macrophages (Fig. 9.16). It can contain scattered bizarre stromal cells that may lead to confusion with a malignant neoplasm, particularly if the previous hysterectomy has been performed due to a malignant tumour.

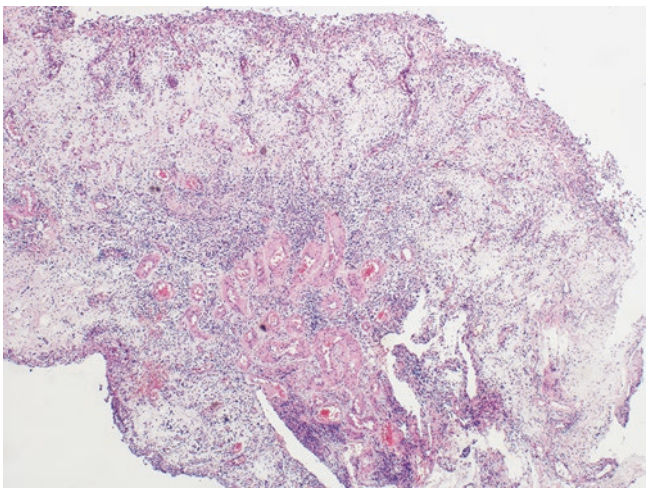

Fig. 9.16 Granulation tissue. Polypoid arrangement of granulation tissue with stromal oedema, pronounced vascularization and multiple mixed inflammatory cells

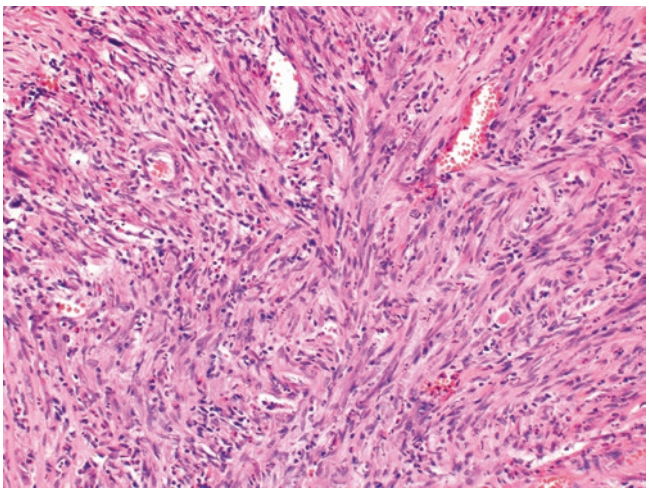

Fig. 9.17 Postoperative spindle cell nodule. The lesion consists of proliferation of spindle cells with bland nuclei, forming fascicles. Scattered inflammatory cells are present in the background

9.3.9 Postoperative Spindle Cell Nodule

9.3.9.1 General and Clinical Features

The postoperative spindle cell nodule (PSCN) is a rare benign lesion of the lower urogenital tract, mostly occurring in the urinary bladder [127]. The lesion is mostly preceded by instrumentation, usually a surgical procedure, and arises within 1–3 months after surgery (in the upper vagina it usually follows a vaginal hysterectomy, whereas in the lower vagina it usually follows an episiotomy). However, cases without such association may occur.

9.3.9.2 Gross and Microscopic Features

Grossly, they are soft sessile or polypoid masses that are typically less than 5 cm in greatest dimension. Microscopically, the lesion consists of the non-neoplastic proliferation of spindle cells forming intersecting fascicles, small blood vessels, myxoid stroma and scattered various inflammatory cells (Fig. 9.17) [127, 128]. The lesional cells show bland nuclei. Mitotic activity can be brisk (more than 25 mitoses/10 HPF); however, no atypical mitoses should be present. Immunohistochemically, the lesions express vimentin, actin and cytokeratins in most cases, in about 50% of cases desmin and rarely EMA. It is usually poorly circumscribed and may infiltrate the adjacent tissue to a limited degree. There may be superficial ulceration, acute superficial and deeper chronic inflammatory cells scattered within the lesion, along with foci of haemorrhage and oedema.

9.3.9.3 Differential Diagnosis

The most important differential diagnosis includes sarcomatoid carcinoma, sarcoma and inflammatory myofibroblastic tumour (IMT). The distinguishing between PSCN and sarcomatoid carcinoma can be difficult, as the lesions share some morphological and immunohistochemical features; however, in contrast to PSCN, sarcomatoid carcinoma is characterized by the presence of markedly atypical spindle cells, atypical mitoses and actin negativity. Other tumours in the differential diagnosis include sarcomas, especially leiomyosarcoma and Kaposi sarcoma. These tumours are also characterized by the presence of nuclear atypia and possibly atypical mitoses. The distinction between PSCN and IMT is controversial [129]. Both lesions showed significant morphological and immunohistochemical overlap, including the possibility of ALK-1 overexpression [130]. Some authors prefer the term "pseudosarcomatous myofibroblastic proliferation", encompassing both IMT and PSCN [130]. However, this is disputable as IMT is usually not associated with any previous surgery and in about 1/3 of cases can recur. Recurrence is not a feature characteristic of PSCN. Moreover, PSCN is usually small (<1 cm) and IMTs tend to be larger.

9.3.10 Prolapsed Fallopian Tube

Fallopian tube prolapse is an uncommon complication caused by either an abdominal or, more commonly, a transvaginal hysterectomy. The patients usually present with pain, vaginal discharge or bleeding. During colposcopy, a red haemorrhagic granular mass can be visible in the vaginal vault, resembling granulation tissue or a tumour [131]. Histologically, the tissue is composed of complex epithelial proliferation, which is commonly polypoid, with tubular and papillary pattern and inflammation in the fibrovascular stroma. The fimbriae are usually not apparent. The epithelial cells are typical of the fallopian tube, including the ciliary,

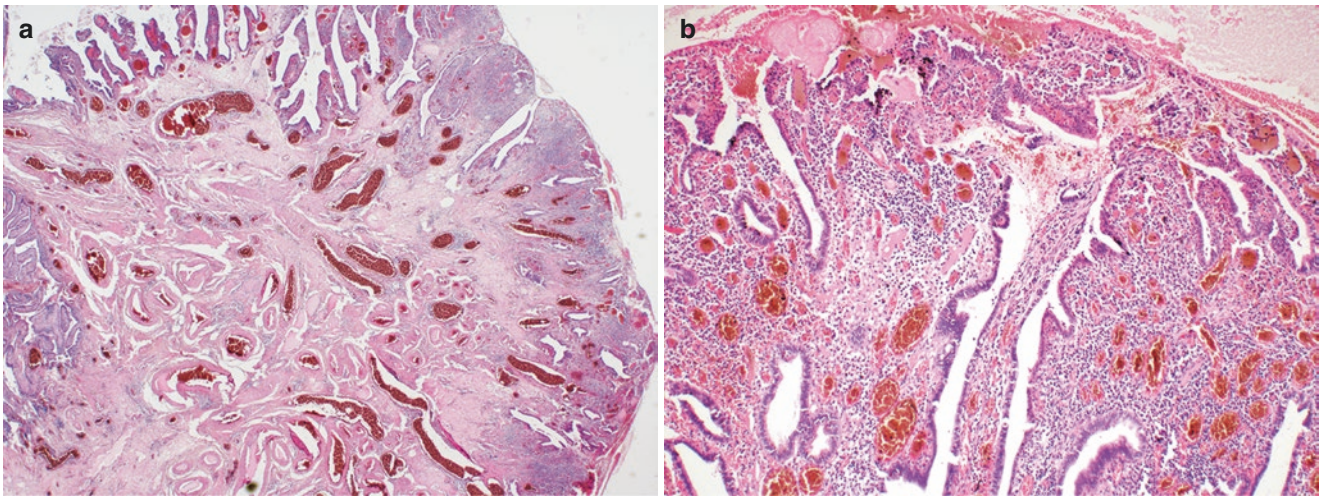

Fig. 9.18 Fallopian tube prolapse. Polypous arrangement of prolapsed Fallopian tube with partly blunted plicae (**a**). The architecture of normal tube is distorted; however, the epithelium is typical of Fallopian tube with the predominance of secretory- and ciliated-type cells (**b**)

secretory and intercalated cells. The differential diagnosis includes endometriosis, vaginal adenosis and primary or metastatic adenocarcinomas. The most important differential diagnosis is against the adenocarcinoma. In this context, the history of the hysterectomy is helpful. Microscopically, the presence of underlying smooth muscle bundles and typical fallopian tube epithelium is characteristic; however, distortion of the normal fallopian tube structure is usually present, including degenerative changes, nuclear crowding, atypia and epithelial hyperplasia due to chronic irritation and inflammation (Fig. 9.18a, b). In these cases, achieving a correct diagnosis can be more difficult [132, 133].

9.3.11 Vaginal Stromal Sclerosis

Vaginal stromal sclerosis represents a change which may be associated with vaginal atrophy [134]. Clinically, it is characterized by the presence of single or multiple plaques or nodules which are firm in consistency. Histologically, the characteristic feature is stromal sclerosis with prominent elastosis, merging imperceptibly with surrounding stroma without an apparent "grenz zone". This can be helpful in the differential diagnosis of some benign stromal tumours occurring in this area, such as myofibroblastoma. Other entities should be considered as well, including amyloidosis and ligneous vaginitis. Amyloidosis of the vagina is usually part of a generalized disease; however, it rarely can occur as a localized disease [135]. Special stains (Congo red, Sirius red) will rule out this possibility. Ligneous vaginitis can occur in patients with plasminogen deficiency [136]. Histologically, homogenous, eosinophilic, fibrin-rich deposits in subepithelial and/or perivascular location are present, associated with chronic inflammatory changes [137].

9.3.12 Fibroepithelial Polyps

9.3.12.1 General and Clinical Features

Fibroepithelial polyps (FP) of the vagina are benign, uncommon lesions that are cured by simple excisions [138, 139]. Approximately 20–25% of FP occurs in pregnant patients, and about 10% of patients have a history of hormonal therapy. The pathogenesis is not well understood, but these lesions probably represent a reactive hyperplastic process which can be hormonally dependent [140]. Most cases are hypocellular, and in these cases, the diagnosis is usually straightforward; however, there are some histologic features which can be suspicious of malignancy, including hypercellularity, increased mitotic activity, atypical mitoses and nuclear atypia.

9.3.12.2 Gross and Microscopic Features

Mostly, these lesions are solitary but may occasionally be multiple. Most lesions are less than 4 cm in greatest dimension, although occasional polyps may be as large as 10 cm. Microscopically, the lesions consist of stromal and epithelial component (Fig. 9.19a–d). The epithelial component, composed of stratified squamous epithelium, is usually intact but may be hyperplastic (i.e. with acanthosis and/or hyperkeratosis). The stromal component shows a much more potentially variable appearance. Typically, the stroma is hypocellular and oedematous, with prominent vessels. Rarely, the stroma can be myxoid. Stromal cells are spindle or stellated and commonly multinucleated. In some cases, nuclear atypia may be present including bizarre hyperchromatic or vesicular nuclei. Increased mitotic activity of more than ten mitoses per ten high-power fields can be found, including atypical mitoses. Cases associated with increased stromal cellularity are designated as "cellular pseudosarco-

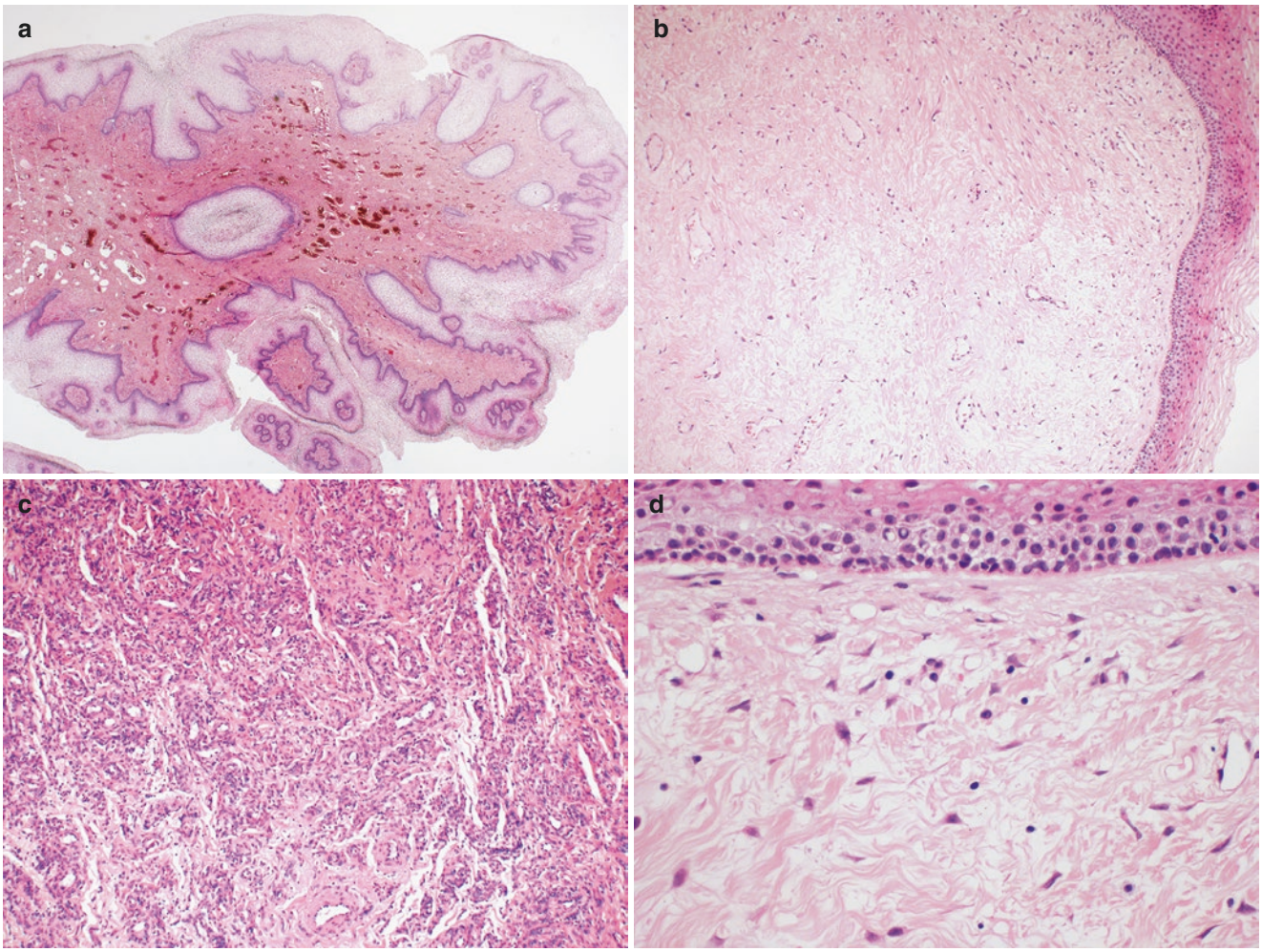

Fig. 9.19 Fibroepithelial polyp. The lesion consists of epithelial component of hyperplastic squamous epithelium and a stromal component (**a**). The stromal component can be variably cellular, ranging from hypocellular (commonly with stromal oedema (**b**)) to hypercellular with pronounced vascularity (**c**). The characteristic stromal cells are spindle or stellated and can be multinucleated (**d**). No grenz zone can be seen

matous fibroepithelial stromal polyps" and occur commonly, but not invariably, during pregnancy [140].

9.3.12.3 Differential Diagnosis

The differential diagnosis of FE with atypical cells and increased cellularity encompasses sarcomas, especially leiomyosarcoma, rhabdomyosarcoma, low-grade endometrial stromal sarcoma, malignant peripheral nerve sheath tumour and dermatofibrosarcoma protuberans. Other neoplasms in the differential diagnosis include tumours belonging to the category of benign stromal tumours of the lower female genital tract, such as aggressive angiomyxoma, cellular angiofibroma, superficial angiomyxoma and myofibroblastoma. Features which help us to achieve the correct diagnosis include (1) presence of multinucleated cells, which are rare in sarcomas; (2) absence of "cambium" layer, typical, for example, for rhabdomyosarcoma; (3) absence of sharp boundary (grenz zone) with the surrounding stroma; (4) exophytic polypous growth of FP; and (5) age of the patient (e.g. sarcoma botryoides usually occurs in children of up to 5 years of age). Immunohistochemistry is generally not very helpful, but in the above-mentioned differential diagnosis, it can be beneficial. The stromal cells of FE polyps are usually desmin and vimentin positive and only rarely smooth muscle actin positive. Expression of estrogen and progesterone receptors is common. Very rarely, the stromal cells of FP may express myogenin, but the pattern of expression is typically restricted, as compared with the diffuse expression that would be expected in rhabdomyosarcoma. FP is also discussed in Chap. 8.

9.3.13 Tubulosquamous Polyp

9.3.13.1 General and Clinical Features

Tubulosquamous polyps are benign lesions that are usually diagnosed in postmenopausal or perimenopausal patients.

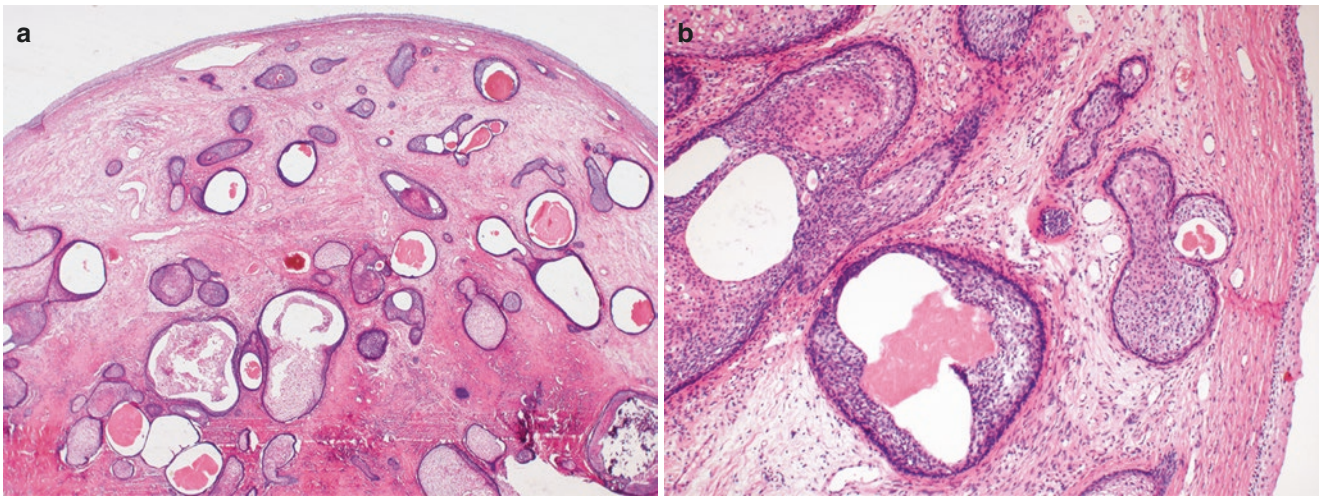

Fig. 9.20 Tubulosquamous polyp. Polypous arrangement of the lesion with apparent epithelial and stromal component (**a**). The epithelial component consists of sharply demarcated nests of cells which are squamous or squamous-transitional in type. Focal tubules can be seen (**b**)

They most commonly occur in the upper vagina and are usually less than 5 cm.

9.3.13.2 Gross and Microscopic Features

Tubulosquamous polyps represent a distinctive entity that is characterized by an admixture of epithelial and stromal components (Fig. 9.20a, b) [141]. The stromal component is in most cases fibrous and rather hypocellular. The epithelial component consists of well-demarcated nests of cells, which are predominantly squamous or squamo-transitional in type, with a minor component of tubules. The tubules are usually small and located at the periphery of squamous nests but may be placed more centrally as well. These tubules are lined by cuboidal cells with scarce clear or eosinophilic cytoplasm [141, 142]. There are also reports of unusual variants of tubulosquamous polyp with a basaloid epithelial component and the presence of sebaceous, mucinous and goblet-cell differentiation [143–145]. Common finding in the glandular component is the immunohistochemical expression of PSA of PrAP [141, 146]. Given this fact, possible histogenetic theories include an origin in [or differentiation towards] ectopic prostatic glands or paraurethral Skene glands [141].

9.3.13.3 Differential Diagnosis

The differential diagnosis for tubulosquamous polyps includes fibroepithelial polyp, vaginal Brenner tumour and mixed tumour of the vagina (spindle cell epithelioma).

Spindle cell epithelioma is also composed of an admixture of epithelial and stromal elements [147]. However, in this entity the stromal component predominates and consists of numerous spindle cells without atypia, which are usually strongly immunoreactive for cytokeratins. In addition, this tumour is usually well circumscribed and occurs in young to middle-aged women, with a predilection for the hymenal region. In contrast, tubulosquamous polyps show a predominance of epithelial cells and the stroma is usually hypocellular. Moreover, the stromal component is cytokeratin negative, and the lesions are usually non-circumscribed and occur in older females, in the upper part of the vagina.

Vaginal Brenner tumour has been rarely reported [148]. Based on the morphology of the reported cases, it is probable that at least some of them could represent tubulosquamous polyp with transitional rather than squamous morphology.

9.3.14 Endocervicosis

By definition, endocervicosis is characterized by the presence of benign glands of endocervical type (probably arising from pelvic or abdominal peritoneum) which are found in ectopic sites, mostly the urinary bladder. Rarely, the cervix, pelvic peritoneum and lymph nodes may also be involved [149, 150]. In the vagina, only two cases have been described, one of them being associated with adenocarcinoma [151, 152].

9.3.15 Endometriosis

Vaginal endometriosis is uncommon and occurs in about 2% of patients with surgically confirmed endometriosis [153]. Based on its location, it can be divided into superficial and deep endometriosis [154]. Superficial endometriosis is associated with direct implantation of endometrial tissue fragments and typically affects the vaginal vault or vaginal stump. Usually, this type of endometriosis is located in areas of prior traumatization, including surgical procedures such as hysterectomy. More common is deep

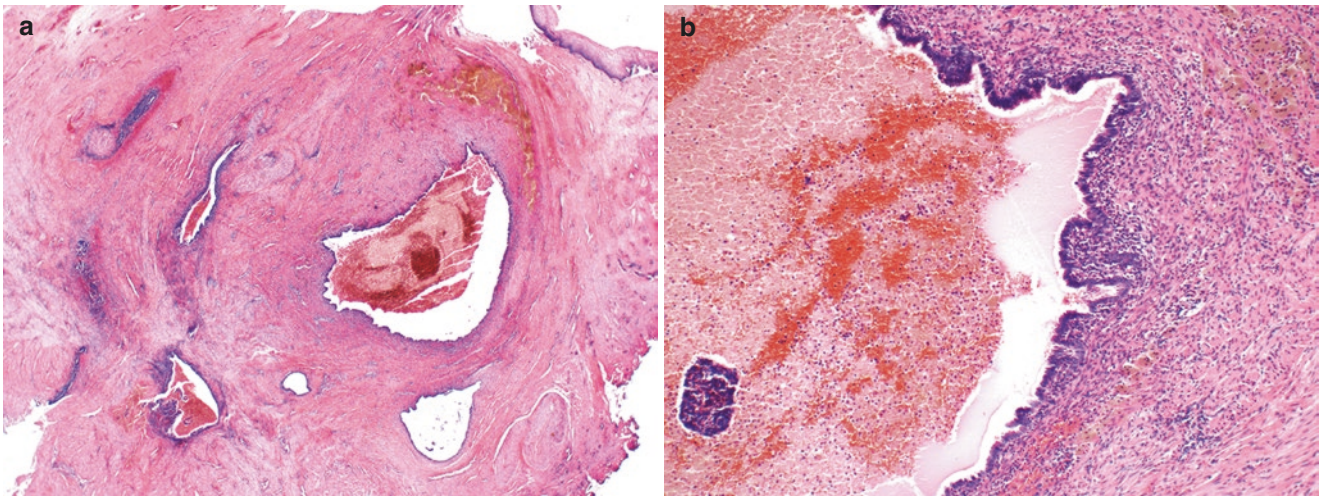

Fig. 9.21 Endometriosis. Presence of endometrial glands and stroma in the vaginal wall (**a**). Inside the dilated endometrial gland, haemolysed blood can be seen. In the surrounding stroma, groups of siderophages with mild inflammatory infiltration are present (**b**)

vaginal endometriosis, which is typically associated with pelvic endometriosis and involves the posterior vaginal fornix. Vaginal endometriosis, as endometriosis in other locations, can give rise to malignant tumours including endometrioid and clear cell carcinoma, adenosarcoma, carcinosarcoma and endometrial stromal sarcoma [155, 156].

Histologically, vaginal endometriosis shows the same features as endometriosis in other locations (Fig. 9.21a, b). Typically there is the presence of both endometrial glands and endometrial stroma, although this is not always the case. Secondary changes such as bleeding and an inflammatory reaction can occur. The diagnosis is usually straightforward; however, in certain cases it may be complicated by secondary changes obscuring the stromal component. In such cases the differential diagnosis of superficial endometriosis and vaginal adenosis can be difficult. The possibility of adenocarcinoma should also be ruled out, especially in cases of deeply infiltrative endometriosis.

9.3.16 Vaginal Adenosis

9.3.16.1 General and Clinical Features

The most common and currently well-known cause of vaginal adenosis is in utero exposure to oral non-steroidal estrogens, such as diethylstilbestrol (DES). The use of these estrogens started in the late 1940s, and before this era, vaginal adenosis was rarely diagnosed [157]. The increased incidence of clear cell adenocarcinoma (CCA) in the offspring of women treated by non-steroidal estrogens during pregnancy led, during the 1970s, to the discovery of the association between these estrogens and both vaginal adenosis and CCA [158].

Vaginal adenosis occurs in 30–45% of women with intrauterine exposure to DES. Experimental studies have shown that the effect of DES is probably related to the influence on urogenital sinus, from which the stratified squamous epithelium (forming the squamous plate in the upper thirds of vagina) arises. Moreover, there is a blockage of the normal segregation of the stroma into the inner and outer layers in the upper genital tract [159, 160]. This knowledge was soon followed by the cessation of non-steroidal estrogen use during pregnancy, and vaginal adenosis related to DES exposure is not a serious issue anymore. Today, vaginal adenosis can occur sporadically in women without any known risk factors, and its incidence has been estimated between 2 and 10% of women. However, adenosis may also be associated with some local therapeutical procedures associated with mucosal injury, such as CO_2 laser vaporization or topical 5-fluorouracil treatment. The etiopathogenetic mechanism of this type of adenosis remains unknown. A possible association between tamoxifen therapy and adenosis has also been described [161].

9.3.16.2 Gross and Microscopic Features

Most cases of adenosis occur in the upper third of the vagina; however, the lesion may occur in the middle and rarely the lower third of the vagina as well. Three main types of adenosis have been described, based on their microscopic features. The most common is endocervical mucinous adenosis, characterized by the presence of endocervical-type mucinous epithelium, which accounts for about 60–75% of cases (Fig. 9.22a, b) [162]. The second type is tuboendometrial adenosis, which is characterized by epithelium with features of endometrial or tubal cells and accounts for about 20% of cases. Rarely, the third type of adenosis may be encountered, consisting of smaller cubic cells usually arranged in small

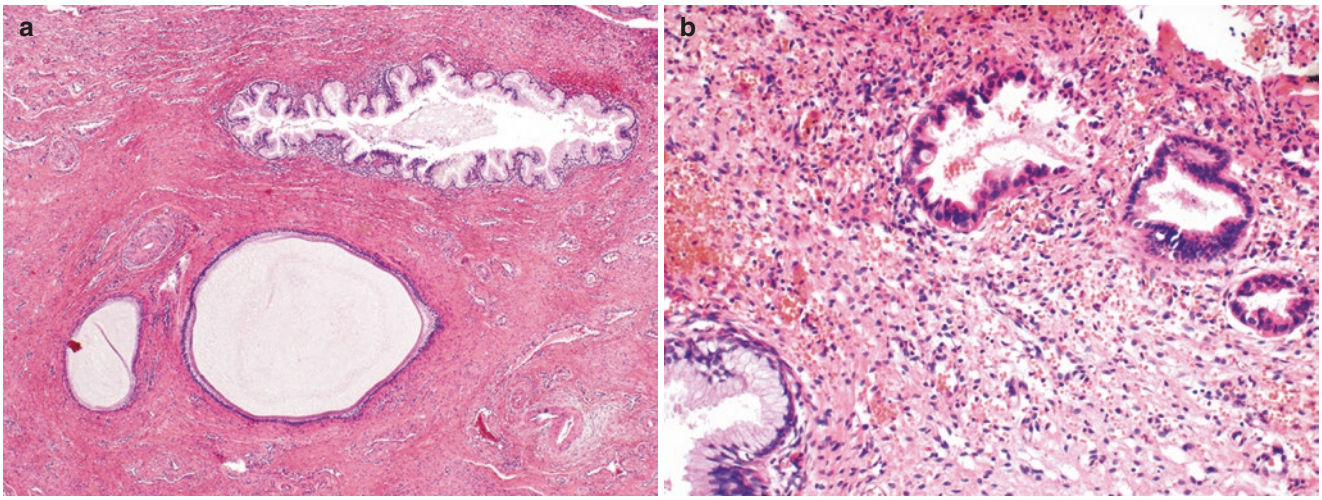

Fig. 9.22 Vaginal adenosis. Mucinous type of adenosis characterized by endocervical-type epithelium with bland nuclear features (**a**). Endometrioid type of adenosis (upper right) consists of smaller glands formed by cells with eosinophilic cytoplasm (**b**)

tubules. Additionally, rare cases of adenosis with intestinal metaplasia have been described [163, 164].

Typically, adenosis affects the superficial vaginal wall, i.e. surface mucosa and/or lamina propria. According to one study, the surface mucosa is involved in about 75% of cases [165]. Adenosis, especially its tuboendometrial variant, may also be located in the lamina propria only. The architecture of adenosis varies from simple glands, which can be cystically dilated, to more complex glandular proliferation. Common change occurring in the areas of adenosis is squamous metaplasia, which can be extensive and can lead to a complete replacement of the antecedent glandular epithelium [166].

9.3.16.3 Atypical Adenosis

Atypical adenosis is characterized by adenosis concurrent with nuclear atypia, including their enlargement, hyperchromasia, irregularity in size and shape, prominent nucleoli and increased mitotic activity. Most cases of atypical adenosis are of the tuboendometrial type [167, 168]. Due to the common association of atypical adenosis with adenocarcinoma, extensive sampling is needed to rule out any presence of invasive growth.

9.3.16.4 Differential Diagnosis

The differential diagnosis of adenosis includes endometriosis, endocervicosis and well-differentiated adenocarcinomas. Endometriosis can be distinguished based on the presence of endometrial stroma, signs of repeated bleeding and, in cases affecting the deeper parts of the vagina, location. Endocervicosis is exceedingly rare and typically affects the deeper parts of the vaginal wall. Well-differentiated adenocarcinoma is usually easily recognized, based on the infiltrative growth pattern and presence of atypia and mitoses.

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References

1. Weber AM, Walters MD, Schover LR, Mitchinson A. Vaginal anatomy and sexual function. Obstet Gynecol. 1995;86(6):946–9.
2. Levin RJ. Sex and the human female reproductive tract--what really happens during and after coitus. Int J Impot Res. 1998;10(Suppl 1):S14–21.
3. Hodgins MB, Spike RC, Mackie RM, MacLean AB. An immunohistochemical study of androgen, oestrogen and progesterone receptors in the vulva and vagina. Br J Obstet Gynaecol. 1998;105(2):216–22.
4. Miyagawa S, Iguchi T. Epithelial estrogen receptor 1 intrinsically mediates squamous differentiation in the mouse vagina. Proc Natl Acad Sci U S A. 2015;112(42):12986–91.
5. Blakeman PJ, Hilton P, Bulmer JN. Cellular proliferation in the female lower urinary tract with reference to oestrogen status. BJOG. 2001;108(8):813–6.
6. Bachmann GA, Nevadunsky NS. Diagnosis and treatment of atrophic vaginitis. Am Fam Physician. 2000;61(10):3090–6.
7. Simon JA. Identifying and treating sexual dysfunction in postmenopausal women: the role of estrogen. J Womens Health (Larchmt). 2011;20(10):1453–65.
8. Kurman RJ. Blaustein's pathology of the female genital tract. New York: Springer; 2011.
9. Miller EA, Beasley DE, Dunn RR, Archie EA. Lactobacilli dominance and vaginal pH: why is the human vaginal microbiome unique? Front Microbiol. 2016;7:1936.
10. Fettweis JM, Serrano MG, Girerd PH, Jefferson KK, Buck GA. A new era of the vaginal microbiome: advances using next-generation sequencing. Chem Biodivers. 2012;9(5):965–76.
11. Kovachev S. Defence factors of vaginal lactobacilli. Crit Rev Microbiol. 2018;44(1):31–9.
12. Kurman RJ, Hedrick Ellenson L, Ronnett BM. Blaustein's pathology of the female genital tract. 6th ed. New York: Springer; 2011. p. 1246.

13. Bertuccini L, Russo R, Iosi F, Superti F. Effects of Lactobacillus rhamnosus and Lactobacillus acidophilus on bacterial vaginal pathogens. Int J Immunopathol Pharmacol. 2017;30(2):163–7.
14. Nwankwo TO, Aniebue UU, Umeh UA. Syndromic diagnosis in evaluation of women with symptoms of vaginitis. Curr Infect Dis Rep. 2017;19(1):3.
15. Mills BB. Vaginitis: beyond the basics. Obstet Gynecol Clin N Am. 2017;44(2):159–77.
16. Cauci S, Driussi S, De Santo D, Penacchioni P, Iannicelli T, Lanzafame P, et al. Prevalence of bacterial vaginosis and vaginal flora changes in peri- and postmenopausal women. J Clin Microbiol. 2002;40(6):2147–52.
17. Cauci S, Monte R, Driussi S, Lanzafame P, Quadrifoglio F. Impairment of the mucosal immune system: IgA and IgM cleavage detected in vaginal washings of a subgroup of patients with bacterial vaginosis. J Infect Dis. 1998;178(6):1698–706.
18. Gravett MG, Nelson HP, DeRouen T, Critchlow C, Eschenbach DA, Holmes KK. Independent associations of bacterial vaginosis and Chlamydia trachomatis infection with adverse pregnancy outcome. JAMA. 1986;256(14):1899–903.
19. Hillier SL, Nugent RP, Eschenbach DA, Krohn MA, Gibbs RS, Martin DH, et al. Association between bacterial vaginosis and preterm delivery of a low-birth-weight infant. The Vaginal Infections and Prematurity Study Group. N Engl J Med. 1995;333(26):1737–42.
20. Morris M, Nicoll A, Simms I, Wilson J, Catchpole M. Bacterial vaginosis: a public health review. BJOG. 2001;108(5):439–50.
21. Gillet E, Meys JF, Verstraelen H, Verhelst R, De Sutter P, Temmerman M, et al. Association between bacterial vaginosis and cervical intraepithelial neoplasia: systematic review and meta-analysis. PLoS One. 2012;7(10):e45201.
22. Nucci MR, Oliva E. In: Goldblum JR, editor. Gynecologic pathology, vol. 592. 1st ed. Spain: Churchill Livingstone; 2009.
23. Bitew A, Abebaw Y, Bekele D, Mihret A. Prevalence of bacterial vaginosis and associated risk factors among women complaining of genital tract infection. Int J Microbiol. 2017;2017:4919404.
24. Gaydos CA, Beqaj S, Schwebke JR, Lebed J, Smith B, Davis TE, et al. Clinical validation of a test for the diagnosis of vaginitis. Obstet Gynecol. 2017;130(1):181–9.
25. Amsel R, Totten PA, Spiegel CA, Chen KC, Eschenbach D, Holmes KK. Nonspecific vaginitis. Diagnostic criteria and microbial and epidemiologic associations. Am J Med. 1983;74(1):14–22.
26. Nugent RP, Krohn MA, Hillier SL. Reliability of diagnosing bacterial vaginosis is improved by a standardized method of gram stain interpretation. J Clin Microbiol. 1991;29(2):297–301.
27. Sodhani P, Garg S, Bhalla P, Singh MM, Sharma S, Gupta S. Prevalence of bacterial vaginosis in a community setting and role of the pap smear in its detection. Acta Cytol. 2005;49(6):634–8.
28. Sodhani P, Gupta S, Gupta R, Mehrotra R. Bacterial vaginosis and cervical intraepithelial neoplasia: is there an association or is co-existence incidental? Asian Pac J Cancer Prev. 2017;18(5):1289–92.
29. Donders GGG, Bellen G, Grinceviciene S, Ruban K, Vieira-Baptista P. Aerobic vaginitis: no longer a stranger. Res Microbiol. 2017;168(9–10):845–58.
30. Donders G, Bellen G, Rezeberga D. Aerobic vaginitis in pregnancy. BJOG. 2011;118(10):1163–70.
31. Rumyantseva TA, Bellen G, Savochkina YA, Guschin AE, Donders GG. Diagnosis of aerobic vaginitis by quantitative real-time PCR. Arch Gynecol Obstet. 2016;294(1):109–14.
32. Geng N, Wu W, Fan A, Han C, Wang C, Wang Y, et al. Analysis of the risk factors for aerobic vaginitis: a case-control study. Gynecol Obstet Investig. 2016;81:148–54.
33. Han C, Wu W, Fan A, Wang Y, Zhang H, Chu Z, et al. Diagnostic and therapeutic advancements for aerobic vaginitis. Arch Gynecol Obstet. 2015;291(2):251–7.
34. Fan A, Yue Y, Geng N, Zhang H, Wang Y, Xue F. Aerobic vaginitis and mixed infections: comparison of clinical and laboratory findings. Arch Gynecol Obstet. 2013;287(2):329–35.
35. Jahic M, Mulavdic M, Nurkic J, Jahic E, Nurkic M. Clinical characteristics of aerobic vaginitis and its association to vaginal candidiasis, trichomonas vaginitis and bacterial vaginosis. Med Arch. 2013;67(6):428–30.
36. Sonnex C. Genital streptococcal infection in non-pregnant women: a case-note review. Int J STD AIDS. 2013;24(6):447–8.
37. Regan JA, Klebanoff MA, Nugent RP, Eschenbach DA, Blackwelder WC, Lou Y, et al. Colonization with group B streptococci in pregnancy and adverse outcome. VIP Study Group. Am J Obstet Gynecol. 1996;174(4):1354–60.
38. Leclair CM, Hart AE, Goetsch MF, Carpentier H, Jensen JT. Group B streptococcus: prevalence in a non-obstetric population. J Low Genit Tract Dis. 2010;14(3):162–6.
39. Savini V, Marrollo R, D'Antonio M, D'Amario C, Fazii P, D'Antonio D. Streptococcus agalactiae vaginitis: nonhemolytic variant on the Liofilchem(R) Chromatic StreptoB. Int J Clin Exp Pathol. 2013;6(8):1693–5.
40. Verkaeren E, Epelboin L, Epelboin S, Boddaert N, Brossier F, Caumes E. Recurrent Streptococcus pyogenes genital infection in a woman: test and treat the partner! Int J Infect Dis. 2014;29:37–9.
41. Verstraelen H, Verhelst R, Vaneechoutte M, Temmerman M. Group A streptococcal vaginitis: an unrecognized cause of vaginal symptoms in adult women. Arch Gynecol Obstet. 2011;284(1):95–8.
42. Meltzer MC, Schwebke JR. Lactational amenorrhea as a risk factor for group a streptococcal vaginitis. Clin Infect Dis. 2008;46(10):e112–5.
43. Chua WC, Mazlan MZ, Ali S, Che Omar S, Wan Hassan WMN, Seevaunnantum SP, et al. Post-partum streptococcal toxic shock syndrome associated with necrotizing fasciitis. IDCases. 2017;9:91–4.
44. Shalaby T, Anandappa S, Pocock NJ, Keough A, Turner A. Lesson of the month 2: toxic shock syndrome. Clin Med (Lond). 2014;14(3):316–8.
45. Schlievert PM, Nemeth KA, Davis CC, Peterson ML, Jones BE. Staphylococcus aureus exotoxins are present in vivo in tampons. Clin Vaccine Immunol. 2010;17(5):722–7.
46. MacPhee RA, Miller WL, Gloor GB, McCormick JK, Hammond JA, Burton JP, et al. Influence of the vaginal microbiota on toxic shock syndrome toxin 1 production by Staphylococcus aureus. Appl Environ Microbiol. 2013;79(6):1835–42.
47. Vostral SL. Rely and toxic shock syndrome: a technological health crisis. Yale J Biol Med. 2011;84(4):447–59.
48. Bhagat N, Karthikeyan A, Kalkur S. Toxic shock syndrome within 24 H of an office hysteroscopy. J Midlife Health. 2017;8(2):92–4.
49. McDermott C, Sheridan M. Staphylococcal toxic shock syndrome caused by tampon use. Case Rep Crit Care. 2015;2015:640373.
50. Ameen F, Moslem M, Al Tami M, Al-Ajlan H, Al-Qahtani N. Identification of Candida species in vaginal flora using conventional and molecular methods. J Mycol Med. 2017;27(3):364–8.
51. Kalaiarasan K, Singh R, Chaturvedula L. Fungal profile of vulvovaginal Candidiasis in a Tertiary Care Hospital. J Clin Diagn Res. 2017;11(3):DC06–DC9.
52. Mtibaa L, Fakhfakh N, Kallel A, Belhadj S, Belhaj Salah N, Bada N, et al. Vulvovaginal candidiasis: etiology, symptomatology and risk factors. J Mycol Med. 2017;27(2):153–8.
53. Nakamura-Vasconcelos SS, Fiorini A, Zanni PD, Bonfim-Mendonca PS, Godoy JR, Almeida-Apolonio AA, et al. Emergence of Candida glabrata in vulvovaginal candidiasis should be attributed to selective pressure or virulence ability? Arch Gynecol Obstet. 2017;296(3):519–26.
54. Mandelblat M, Frenkel M, Abbey D, Ben Ami R, Berman J, Segal E. Phenotypic and genotypic characteristics of Candida albicans isolates from bloodstream and mucosal infections. Mycoses. 2017;60(8):534–45.

55. Matheson A, Mazza D. Recurrent vulvovaginal candidiasis: a review of guideline recommendations. Aust N Z J Obstet Gynaecol. 2017;57(2):139–45.
56. Cauchie M, Desmet S, Lagrou K. Candida and its dual lifestyle as a commensal and a pathogen. Res Microbiol. 2017;168(9–10):802–10.
57. Yano J, Noverr MC, Fidel PL Jr. Vaginal heparan sulfate linked to neutrophil dysfunction in the acute inflammatory response associated with experimental vulvovaginal candidiasis. MBio. 2017;8:2.
58. Asia AJ, Tapre VN. Primary actinomycosis of vulva with inguinal lymphadenopathy. Indian Dermatol Online J. 2016;7(5):402–5.
59. Hagiya H, Ogawa H, Takahashi Y, Kimura K, Hasegawa K, Otsuka F. Actinomyces turicensis bacteremia secondary to pyometra. Intern Med. 2015;54(21):2775–7.
60. Khodavaisy S, Zibafar E, Hashemi SJ, Narenji H, Daie Ghazvini R. Actinomycosis in Iran: short narrative review article. Iran J Public Health. 2014;43(5):556–60.
61. Arora BB, Maheshwari M, Devgan N, Arora DR. Prevalence of trichomoniasis, vaginal candidiasis, genital herpes, chlamydiasis, and actinomycosis among urban and rural women of Haryana, India. J Sex Transm Dis. 2014;2014:963812.
62. Mutter GL, Prat J. Pathology of the female reproductive tract. 3rd ed. Spain: Churchill Livingstone; 2014. p. 904.
63. Yilmaz M, Akbulut S, Samdanci ET, Yilmaz S. Abdominopelvic actinomycosis associated with an intrauterine device and presenting with a rectal mass and hydronephrosis: a troublesome condition for the clinician. Int Surg. 2012;97(3):254–9.
64. Westhoff C. IUDs and colonization or infection with Actinomyces. Contraception. 2007;75(6 Suppl):S48–50.
65. Clement PB, Young RH. Atlas of gynecologic surgical pathology. 3rd ed. Philadelphia, PA: Saunders; 2013. p. 584.
66. Kaya D, Demirezen S, Hascelik G, Gulmez Kivanc D, Beksac MS. Comparison of PCR, culturing and Pap smear microscopy for accurate diagnosis of genital Actinomyces. J Med Microbiol. 2013;62(Pt 5):727–33.
67. Edwards T, Burke P, Smalley H, Hobbs G. Trichomonas vaginalis: clinical relevance, pathogenicity and diagnosis. Crit Rev Microbiol. 2016;42(3):406–17.
68. Fichorova R, Fraga J, Rappelli P, Fiori PL. Trichomonas vaginalis infection in symbiosis with Trichomonasvirus and Mycoplasma. Res Microbiol. 2017;168(9–10):882–91.
69. Fichorova RN. Impact of T. vaginalis infection on innate immune responses and reproductive outcome. J Reprod Immunol. 2009;83(1–2):185–9.
70. Kirkcaldy RD, Augostini P, Asbel LE, Bernstein KT, Kerani RP, Mettenbrink CJ, et al. Trichomonas vaginalis antimicrobial drug resistance in 6 US cities, STD Surveillance Network, 2009–2010. Emerg Infect Dis. 2012;18(6):939–43.
71. Jenniskens ML, Veerbeek JH, Deurloo KL, van Hannen EJ, Thijsen SF. Routine testing of Mycoplasma genitalium and Trichomonas vaginalis. Infect Dis (Lond). 2017;49(6):461–5.
72. Kissinger P. Trichomonas vaginalis: a review of epidemiologic, clinical and treatment issues. BMC Infect Dis. 2015;15:307.
73. Madico G, Quinn TC, Rompalo A, McKee KT Jr, Gaydos CA. Diagnosis of Trichomonas vaginalis infection by PCR using vaginal swab samples. J Clin Microbiol. 1998;36(11):3205–10.
74. Fonseca THS, Oliveira FMS, Alacoque M, Rocha MI, Leite HV, Santos JFG, et al. Immunocytochemistry improving the diagnosis of trichomonas vaginalis infections. Biomed Res Int. 2017;2017:5642535.
75. Van Der Pol B. Sexually transmitted infections in women. Scand J Clin Lab Invest Suppl. 2014;244:68–74. discussion 3
76. Crum CP, Nucci MR, Lee KR. Diagnostic gynecologic and obstetric pathology. 2nd ed. Philadelphia, PA: Elsevier Saunders; 2011. p. 1216.
77. CDC. Sexually transmitted disease surveillance 2014. Atlanta: US Department of Health and Human Services; 2015.
78. Smith L, Angarone MP. Sexually transmitted infections. Urol Clin North Am. 2015;42(4):507–18.
79. Abou M, Dallenbach P. Acute cervicitis and vulvovaginitis may be associated with Cytomegalovirus. BMJ Case Rep. 2013;2013:bcr2013008884.
80. Sobel JD. Gynecologic infections in human immunodeficiency virus-infected women. Clin Infect Dis. 2000;31(5):1225–33.
81. Kemal KS, Foley B, Burger H, Anastos K, Minkoff H, Kitchen C, et al. HIV-1 in genital tract and plasma of women: compartmentalization of viral sequences, coreceptor usage, and glycosylation. Proc Natl Acad Sci U S A. 2003;100(22):12972–7.
82. Herold BC, Keller MJ, Shi Q, Hoover DR, Carpenter CA, Huber A, et al. Plasma and mucosal HIV viral loads are associated with genital tract inflammation in HIV-infected women. J Acquir Immune Defic Syndr. 2013;63(4):485–93.
83. Spear GT, St John E, Zariffard MR. Bacterial vaginosis and human immunodeficiency virus infection. AIDS Res Ther. 2007;4:25.
84. Nardis C, Mosca L, Mastromarino P. Vaginal microbiota and viral sexually transmitted diseases. Ann Ig. 2013;25(5):443–56.
85. Newman L, Rowley J, Vander Hoorn S, Wijesooriya NS, Unemo M, Low N, et al. Global estimates of the prevalence and incidence of four curable sexually transmitted infections in 2012 based on systematic review and global reporting. PLoS One. 2015;10(12):e0143304.
86. Juzlova K, Rob F, Zakoucka H, Kubatova A, Secnikova Z, Krasova M, et al. The first case of lymphogranuloma venereum in a woman in East-Central Europe and its multiple co-infections. Folia Microbiol (Praha). 2018;63(1):93–5.
87. Ceovic R, Gulin SJ. Lymphogranuloma venereum: diagnostic and treatment challenges. Infect Drug Resist. 2015;8:39–47.
88. Gray DJ, Ross AG, Li YS, McManus DP. Diagnosis and management of schistosomiasis. BMJ. 2011;342:d2651.
89. Kjetland EF, Leutscher PD, Ndhlovu PD. A review of female genital schistosomiasis. Trends Parasitol. 2012;28(2):58–65.
90. Kjetland EF, Poggensee G, Helling-Giese G, Richter J, Sjaastad A, Chitsulo L, et al. Female genital schistosomiasis due to Schistosoma haematobium. Clinical and parasitological findings in women in rural Malawi. Acta Trop. 1996;62(4):239–55.
91. Swai B, Poggensee G, Mtweve S, Krantz I. Female genital schistosomiasis as an evidence of a neglected cause for reproductive ill-health: a retrospective histopathological study from Tanzania. BMC Infect Dis. 2006;6:134.
92. Kjetland EF, Kurewa EN, Ndhlovu PD, Midzi N, Gwanzura L, Mason PR, et al. Female genital schistosomiasis--a differential diagnosis to sexually transmitted disease: genital itch and vaginal discharge as indicators of genital Schistosoma haematobium morbidity in a cross-sectional study in endemic rural Zimbabwe. Tropical Med Int Health. 2008;13(12):1509–17.
93. Poggensee G, Feldmeier H. Female genital schistosomiasis: facts and hypotheses. Acta Trop. 2001;79(3):193–210.
94. Helling-Giese G, Sjaastad A, Poggensee G, Kjetland EF, Richter J, Chitsulo L, et al. Female genital schistosomiasis (FGS): relationship between gynecological and histopathological findings. Acta Trop. 1996;62(4):257–67.
95. Midzi N, Ndhlovu PD, Nyanga L, Kjetland EF, Reimert CM, Vennervald BJ, et al. Assessment of eosinophil cationic protein as a possible diagnostic marker for female genital schistosomiasis in women living in a Schistosoma haematobium endemic area. Parasite Immunol. 2003;25(11–12):581–8.
96. Norseth HM, Ndhlovu PD, Kleppa E, Randrianasolo BS, Jourdan PM, Roald B, et al. The colposcopic atlas of schistosomiasis in the lower female genital tract based on studies in Malawi, Zimbabwe, Madagascar and South Africa. PLoS Negl Trop Dis. 2014;8(11):e3229.
97. Dennie J, Grover SR. Distressing perineal and vaginal pain in prepubescent girls: an aetiology. J Paediatr Child Health. 2013;49(2):138–40.

98. Kashyap B, Samantray JC, Kumar S, Jhamb R, Singh AK, Kaur IR. Recurrent paediatric pinworm infection of the vagina as a potential reservoir for Enterobius vermicularis. J Helminthol. 2014;88(3):381–3.
99. Tsai CY, Junod R, Jacot-Guillarmod M, Beniere C, Ziadi S, Bongiovanni M. Vaginal Enterobius vermicularis diagnosed on liquid-based cytology during papanicolaou test cervical cancer screening: a report of two cases and a review of the literature. Diagn Cytopathol. 2018;46(2):179–86.
100. Ngui R, Ravindran S, Ong DB, Chow TK, Low KP, Nureena ZS, et al. Enterobius vermicularis salpingitis seen in the setting of ectopic pregnancy in a Malaysian patient. J Clin Microbiol. 2014;52(9):3468–70.
101. Garden AS. Vulvovaginitis and other common childhood gynaecological conditions. Arch Dis Child Educ Pract Ed. 2011;96(2):73–8.
102. Deshpande AD. Enterobius vermicularis live adult worms in the high vagina. Postgrad Med J. 1992;68(802):690–1.
103. Mehrotra S, Young SL, Wojcik EM. Brown oval structures in vaginal Thin Prep smear: What could they be? Diagn Cytopathol. 2007;35(10):651–2.
104. Raju K, Verappa S, Venkataramappa SM. Enterobius vermicularis infestation masquerading as cervical carcinoma: a cytological diagnosis. J Nat Sci Biol Med. 2015;6(2):476–9.
105. Richens J. Genital manifestations of tropical diseases. Sex Transm Infect. 2004;80(1):12–7.
106. Nopdonrattakoon L. Amoebiasis of the female genital tract: a case report. J Obstet Gynaecol Res. 1996;22(3):235–8.
107. Munguia H, Franco E, Valenzuela P. Diagnosis of genital amebiasis in women by the standard Papanicolaou technique. Am J Obstet Gynecol. 1966;94(2):181–8.
108. Foda AA, El-Malky MM. Prevalence of genital tract infection with Entamoeba gingivalis among copper T 380A intrauterine device users in Egypt. Contraception. 2012;85(1):108–12.
109. Hyun KH, Shin HD, Kim DH. Malakoplakia in a healthy young female patient. Korean J Intern Med. 2013;28(4):475–80.
110. Jimerson SD, Becker JD. Vaginal ulcers associated with tampon usage. Obstet Gynecol. 1980;56(1):97–9.
111. LeRiche T, Black AY, Fleming NA. Toxic shock syndrome of a probable gynecologic source in an adolescent: a case report and review of the literature. J Pediatr Adolesc Gynecol. 2012;25(6):e133–7.
112. Tang YW, Himmelfarb E, Wills M, Stratton CW. Characterization of three Staphylococcus aureus isolates from a 17-year-old female who died of tampon-related toxic shock syndrome. J Clin Microbiol. 2010;48(5):1974–7.
113. Ghoniem GM, Warda HA. The management of genitourinary fistula in the third millennium. Arab J Urol. 2014;12(2):97–105.
114. Morris L, Do V, Chard J, Brand AH. Radiation-induced vaginal stenosis: current perspectives. Int J Womens Health. 2017;9:273–9.
115. Haylen BT, Maher CF, Barber MD, Camargo S, Dandolu V, Digesu A, et al. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic organ prolapse (POP). Int Urogynecol J. 2016;27(2):165–94.
116. Iglesia CB, Smithling KR. Pelvic organ prolapse. Am Fam Physician. 2017;96(3):179–85.
117. Tjugum J, Jonassen F, Olsson JH. Vaginitis emphysematosa in a renal transplant patient. Acta Obstet Gynecol Scand. 1986;65(4):377–8.
118. Gardner HL, Fernet P. Etiology of vaginitis emphysematosa: report of ten cases and review of literature. Am J Obstet Gynecol. 1964;88:680–94.
119. Reichman O, Sobel J. Desquamative inflammatory vaginitis. Best Pract Res Clin Obstet Gynaecol. 2014;28(7):1042–50.
120. Mitchell L, King M, Brillhart H, Goldstein A. Cervical ectropion may be a cause of desquamative inflammatory vaginitis. Sex Med. 2017;5(3):e212–4.
121. Shaw JL, Diamandis EP. A potential role for tissue kallikrein-related peptidases in human cervico-vaginal physiology. Biol Chem. 2008;389(6):681–8.
122. Chen S, Ge R, Zhu L, Yang S, Wu W, Yang Y, et al. Giant primary vaginal calculus secondary to vesicovaginal fistula with partial vaginal outlet obstruction in a 12-year-old girl. Urology. 2011;78(4):908–10.
123. Malhotra N, Kumar S, Roy KK, Agarwal R, Verma V. Vaginal calculus secondary to vaginal outlet obstruction. J Clin Ultrasound. 2004;32(4):204–6.
124. Rahn DD, Carberry C, Sanses TV, Mamik MM, Ward RM, Meriwether KV, et al. Vaginal estrogen for genitourinary syndrome of menopause: a systematic review. Obstet Gynecol. 2014;124(6):1147–56.
125. Pradhan S, Tobon H. Vaginal cysts: a clinicopathological study of 41 cases. Int J Gynecol Pathol. 1986;5(1):35–46.
126. Steinberg BJ, Mapp T, Mama S, Echols KT. Surgical treatment of persistent vaginal granulation tissue using CO(2) laser vaporization under colposcopic and laparoscopic guidance. JSLS. 2012;16(3):488–91.
127. Proppe KH, Scully RE, Rosai J. Postoperative spindle cell nodules of genitourinary tract resembling sarcomas. A report of eight cases. Am J Surg Pathol. 1984;8(2):101–8.
128. Zhao J, Ping H, Xing N. Postoperative spindle cell nodule of the bladder: a case report and review of the literature. Oncol Lett. 2014;7(5):1507–10.
129. Alderman M, Kunju LP. Inflammatory myofibroblastic tumor of the bladder. Arch Pathol Lab Med. 2014;138(10):1272–7.
130. Harik LR, Merino C, Coindre JM, Amin MB, Pedeutour F, Weiss SW. Pseudosarcomatous myofibroblastic proliferations of the bladder: a clinicopathologic study of 42 cases. Am J Surg Pathol. 2006;30(7):787–94.
131. Song YS, Kang JS, Park MH. Fallopian tube prolapse misdiagnosed as vault granulation tissue: a report of three cases. Pathol Res Pract. 2005;201(12):819–22.
132. Silverberg SG, Frable WJ. Prolapse of fallopian tube into vaginal vault after hysterectomy. Histopathology, cytopathology, and differential diagnosis. Arch Pathol. 1974;97(2):100–3.
133. Wheelock JB, Schneider V, Goplerud DR. Prolapsed fallopian tube masquerading as adenocarcinoma of the vagina in a postmenopausal woman. Gynecol Oncol. 1985;21(3):369–75.
134. Fadare O. Vaginal stromal sclerosis: a distinctive stromal change associated with vaginal atrophy. Int J Gynecol Pathol. 2011;30(3):295–300.
135. Pehlivanov B, Belovegdov V, Ivanov G, Ivancheva H. Primary localised amyloidosis of the vagina. Aust N Z J Obstet Gynaecol. 2008;48(1):120–2.
136. Altinkaya SO, Uzunlar O, Talas BB, Ozat M, Bilge U. Ligneous cervicovaginitis. Taiwan J Obstet Gynecol. 2008;47(3):363–6.
137. Chi AC, Prichard E, Richardson MS, Rasenberger KP, Weathers DR, Neville BW. Pseudomembranous disease (ligneous inflammation) of the female genital tract, peritoneum, gingiva, and paranasal sinuses associated with plasminogen deficiency. Ann Diagn Pathol. 2009;13(2):132–9.
138. Nielsen GP, Young RH. Mesenchymal tumors and tumor-like lesions of the female genital tract: a selective review with emphasis on recently described entities. Int J Gynecol Pathol. 2001;20(2):105–27.
139. Norris HJ, Taylor HB. Polyps of the vagina. A benign lesion resembling sarcoma botryoides. Cancer. 1966;19(2):227–32.
140. Nucci MR, Young RH, Fletcher CD. Cellular pseudosarcomatous fibroepithelial stromal polyps of the lower female genital tract: an underrecognized lesion often misdiagnosed as sarcoma. Am J Surg Pathol. 2000;24(2):231–40.
141. McCluggage WG, Young RH. Tubulo-squamous polyp: a report of ten cases of a distinctive hitherto uncharacterized vaginal polyp. Am J Surg Pathol. 2007;31(7):1013–9.

142. Dundr P, Povysil C, Mara M, Kuzel D. Tubulo-squamous polyp of the vagina. Cesk Patol. 2008;44(2):45–7.
143. Chaturvedi A, Padel A. Tubulo-squamous polyp of the vagina with sebaceous glands: novel features in an uncommon recently described entity. Int J Gynecol Pathol. 2010;29(5):494–6.
144. Tong B, Clarke BA, Ghazarian D. Tubulo-squamous polyp with mucinous and goblet cell differentiation: a unique morphologic variant. Int J Gynecol Pathol. 2011;30(5):518–9.
145. Stewart CJ. Tubulo-squamous vaginal polyp with basaloid epithelial differentiation. Int J Gynecol Pathol. 2009;28(6):563–6.
146. Kazakov DV, Stewart CJ, Kacerovska D, Leake R, Kreuzberg B, Chudacek Z, et al. Prostatic-type tissue in the lower female genital tract: a morphologic spectrum, including vaginal tubulosquamous polyp, adenomyomatous hyperplasia of paraurethral Skene glands (female prostate), and ectopic lesion in the vulva. Am J Surg Pathol. 2010;34(7):950–5.
147. Berdugo J, Gauthier P, Provencher D, Matte C, Piche J, Rahimi K. Spindle cell epithelioma of the vagina: report of two cases, literature review, and new immunohistochemical markers. Int J Surg Pathol. 2015;23(8):677–81.
148. Park S, Cho MS. Vaginal Brenner tumor with literature review: does this tumour originate from Walthard nests? Malays J Pathol. 2017;39(1):89–93.
149. Young RH, Clement PB. Endocervicosis involving the uterine cervix: a report of four cases of a benign process that may be confused with deeply invasive endocervical adenocarcinoma. Int J Gynecol Pathol. 2000;19(4):322–8.
150. Clement PB, Young RH. Endocervicosis of the urinary bladder. A report of six cases of a benign mullerian lesion that may mimic adenocarcinoma. Am J Surg Pathol. 1992;16(6):533–42.
151. Martinka M, Allaire C, Clement PB. Endocervicosis presenting as a painful vaginal mass: a case report. Int J Gynecol Pathol. 1999;18(3):274–6.
152. McCluggage WG, Price JH, Dobbs SP. Primary adenocarcinoma of the vagina arising in endocervicosis. Int J Gynecol Pathol. 2001;20(4):399–402.
153. Stern RC, Dash R, Bentley RC, Snyder MJ, Haney AF, Robboy SJ. Malignancy in endometriosis: frequency and comparison of ovarian and extraovarian types. Int J Gynecol Pathol. 2001;20(2):133–9.
154. Gardner HL. Cervical and vaginal endometriosis. Clin Obstet Gynecol. 1966;9(2):358–72.
155. Liu L, Davidson S, Singh M. Mullerian adenosarcoma of vagina arising in persistent endometriosis: report of a case and review of the literature. Gynecol Oncol. 2003;90(2):486–90.
156. Nomoto K, Hori T, Kiya C, Fukuoka J, Nakashima A, Hidaka T, et al. Endometrioid adenocarcinoma of the vagina with a microglandular pattern arising from endometriosis after hysterectomy. Pathol Int. 2010;60(9):636–41.
157. Guercio F. Adenosis of the vagina and its consequences. Arch Ostet Ginecol. 1959;64:588–600.
158. Scully RE, Robboy SJ, Herbst AL. Vaginal and cervical abnormalities, including clear-cell adenocarcinoma, related to prenatal exposure to stilbestrol. Ann Clin Lab Sci. 1974;4(4):222–33.
159. Robboy SJ, Taguchi O, Cunha GR. Normal development of the human female reproductive tract and alterations resulting from experimental exposure to diethylstilbestrol. Hum Pathol. 1982;13(3):190–8.
160. Forsberg JG. Animal model of human disease: adenosis and clear-cell carcinomas of vagina and cervix. Am J Pathol. 1976;84(3):669–72.
161. Ganesan R, Ferryman SR, Waddell CA. Vaginal adenosis in a patient on Tamoxifen therapy: a case report. Cytopathology. 1999;10(2):127–30. discussion 31
162. Goodman A, Zukerberg LR, Nikrui N, Scully RE. Vaginal adenosis and clear cell carcinoma after 5-fluorouracil treatment for condylomas. Cancer. 1991;68(7):1628–32.
163. Lu W, Zhang X, Lu B. Benign intestinal glandular lesions in the vagina: a possible correlation with implantation. Diagn Pathol. 2016;11(1):52.
164. Merchant WJ, Gale J. Intestinal metaplasia in stilboestrol-induced vaginal adenosis. Histopathology. 1993;23(4):373–6.
165. Antonioli DA, Burke L. Vaginal adenosis. Analysis of 325 biopsy specimens from 100 patients. Am J Clin Pathol. 1975;64(5):625–38.
166. Hart WR, Townsend DE, Aldrich JO, Henderson BE, Roy M, Benton B. Histopathologic spectrum of vaginal adenosis and related changes in stilbestrol-exposed females. Cancer. 1976;37(2):763–75.
167. Robboy SJ, Noller KL, O'Brien P, Kaufman RH, Townsend D, Barnes AB, et al. Increased incidence of cervical and vaginal dysplasia in 3,980 diethylstilbestrol-exposed young women. Experience of the National Collaborative Diethylstilbestrol Adenosis Project. JAMA. 1984;252(21):2979–83.
168. Antonioli DA, Rosen S, Burke L, Donahue V. Glandular dysplasia in diethylstilbestrol-associated vaginal adenosis. A case report and review of the literature. Am J Clin Pathol. 1979;71(6):715–21.