Essentials of Diagnostic Gynecological Pathology
Series Editors: Naveena Singh · W. Glenn McCluggage

Laurence Brown *Editor*

Pathology of the Vulva and Vagina

Springer

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This series is dedicated to the respected memory of Professor Harold Fox (1931–2012), one of the foremost gynecological pathologists of all time, in recognition of the ageless legacy of his teaching and written word which will continue to inspire many generations of gynecological pathologists.

Preface to the Series

Gynecological pathology forms a large proportion of the diagnostic workload of most histopathology laboratories. There are frequent changes in diagnostic criteria, ancillary techniques, and staging systems, as well as descriptions of new entities that the diagnostic pathologist needs to keep up to date with, particularly in view of the ever increasing pressure from government, the public, and clinicians for accurate and timely diagnosis. This updating needs to be an individual and continuous exercise of professional development, through reading papers and attending conferences and courses as well as through self-study using published texts.

The female genital tract is a complex system with several different organs. In-depth knowledge of all areas is not necessarily the requirement of all pathologists. Many pathologists have more limited needs; for example, the bulk of the diagnostic work in a United Kingdom district general hospital is formed by cervical screening program-related biopsies, endometrial biopsies, benign uterine pathologies, and miscarriage-related as well as placental pathology, while due to current cancer treatment guidelines, most complex surgical specimens, particularly ovarian, cervical, and vulval cancers, are dealt with in cancer centers. Dermatopathologists may have an interest in vulval pathology but not in other areas of gynecological pathology. Pathology texts are also of interest to researchers and clinicians in particular specialties, for example, dermatologists and oncologists, and their interest will often be restricted to one particular area.

The British Association of Gynecological Pathologists (BAGP) aims to support the development and maintenance of the highest standards of clinical diagnostic practice in gynecological pathology. This aim is achieved through various educational activities, including courses, meetings, and cases of interest on its website, www.thebagp.org. The idea for a series of textbooks, each covering a specific area in gynecological pathology, was conceived while serving within the council of the BAGP. The series is intended for consultant pathologists and trainees who may have a requirement or interest in one or more areas of gynecological pathology due to their particular work situation. These books are intended to provide clear updated information on currently accepted classifications, nomenclature, diagnostic criteria, management implications, staging, and the role of ancillary techniques for neoplastic and nonneoplastic gynecological pathologies. For those interested in all areas of gynecological pathology, this series of smaller individual books holds greater

potential for timely responsiveness to major changes in the field in subsequent editions, by virtue of having multiple contributors and a more limited scope in comparison to larger available texts. Dividing up the field also makes individual volumes more affordable for those in need of access to detailed information in a specific area in gynecological pathology.

We hope that the successive volumes in this series will present the essentials of current diagnostic gynecological pathology comprehensively and in a compact format for practicing and trainee pathologists as well as others.

March 2012

W. Glenn McCluggage
Naveena Singh

Preface to This Volume

The vulva has featured in ritual and Palaeolithic art since the dawn of humanity. Starting with simple line drawings scratched on rock, then evolving into three-dimensional carvings, the vulva is prominent in that apotheosis of the fertility symbol, the Venus of Willendorf [1, 2].

In later history, Sheela-na-gig stylized vulvas, disembodied or not, were a common sight in medieval Europe, placed above the lintels of simple country churches [3]. However, women growing up in most modern societies rarely uncover their vulvas in public, and perhaps because of this, vulval disease tends to be neglected. Groups such as the International Society for the Study of Vulvovaginal Disease (http://www.issvd.org) and the affiliated British Society for the Study of Vulval Disease (http://www.bssvd.org) have been raising awareness of the medical and psychosocial aspects of conditions affecting these sites and are now increasing their attention to the pathological understanding of those diseases.

Yet, of the many gynecological histology specimens received in a routine laboratory, those derived from the vulva or vagina constitute only a small fraction. Vulval diseases are relatively rare and vaginal lesions almost vanishingly so. Though this is possibly one of the factors that make their histological diagnosis problematic—even for specialist gynecological pathologists—this is by no means the only factor. While women readily seek medical advice for symptoms related to vaginal bleeding, discharge, or pelvic symptoms, for psychosocial reasons, they may be more hesitant with a visible lesion or symptoms related to the vulva. Consequently, secondary changes in long-standing lesions, compounded by occlusion, moisture, scratching, and possibly self-medication, are common. Secondly, while many rare, site-specific lesions occurring in the vulva are known to gynecological pathologists, they may be less familiar with dermatological conditions involving vulval skin. Furthermore, recent years have seen the description of many new lesions and refinement in the diagnostic criteria of existing entities.

This book illustrates with stylish artist-drawn graphics the basic anatomy and embryology necessary to understand the range of lesions and symptoms occurring here. The misery of vulval itch, swelling, soreness, or pain is explained by detailed descriptions of the extensive range of tropical and non-tropical infections to affect the site with clear descriptions of the noninfectious dermatological and mucosal dermatoses that may also be seen. The chapter on benign and malignant glandular lesions includes our increasing

awareness of prostatic-like tissues in the lower female genital tract. Recent advances in the understanding of human papilloma virus in the causation of vulval squamous carcinoma, nonviral causes of carcinoma, and the underlying conditions of differentiated VIN, lichen sclerosus, and lichen simplex chronicus are explained at length. Other chapters cover the diagnosis of the earliest stages in the development of squamous carcinoma, the concept of sentinel node biopsy, the mimics of squamous neoplasia, and the wide and often difficult differential diagnoses of soft tissue and melanocytic lesions. A final chapter covers extramammary Paget's disease, outlines the difference to Paget's disease of the breast, and reviews the concept of anogenital mammary type glands and their role in glandular neoplasia in this site.

All these factors and others make the study of vulvovaginal disease interesting but also difficult. Clinically, these conditions may fall within the remit of general practice, gynecology, or dermatology teams. In the approach to the morphological diagnosis of vulvovaginal diseases, the most cogent advice that can be offered is to be aware of these factors and to promote close working between gynecological and dermatological pathologists. The chapters that follow are authored by experts in the pathology of gynecology, dermatology, and genitourinary medicine with exactly these points in mind.

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Naveena Singh
Laurence Brown

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Development and Anatomy: Disorders of Development

1

Naveena Singh

Abstract

An overview of the complex embryological development of the lower female genital tract, some of which remains incompletely understood, is useful for the understanding of many neoplastic and nonneoplastic vulvovaginal lesions. The Fallopian tubes, uterus, and cervix develop from the paramesonephric (Mullerian) ducts. The vagina has a dual origin with the upper portion, including the vaginal fornices, arising from the paramesonephric ducts and the lower portion from the urogenital sinus. The development of the mesoderm surrounding the female genital tract in humans is incompletely understood. Experimental studies demonstrate that complex stromal epithelial interactions are crucial for site-specific epithelial differentiation, especially for development of glandular epithelia. Development of external genitalia occurs under the influence of sex hormones through proliferation of the mesoderm and ectoderm lateral and ventral to the cloaca. The area bounded by the vaginal orifice and the urogenital sinus enlarges to form the vestibule and is of endodermal origin. This is morphologically and functionally distinct from the rest of vulval tissues which are mesodermally and ectodermally derived. This difference in origin is reflected in differences in responses to sex hormones and other stimuli. A variety of abnormalities in development can therefore occur as a result of structural and hormonal disturbances, including external influences such as in utero exposure to diethylstilbestrol.

Development of the Vulva and Vagina

An overview of the embryological development of the lower female genital tract is useful for the understanding of many neoplastic and nonneoplastic lesions that occur at this site. Although there have been many advances in the study of the development of the human embryo, the development of parts of urogenital system remains incompletely understood [1].

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The Fallopian tubes, uterus, and cervix develop from the paramesonephric (Mullerian) ducts. The vagina develops by contributions from the Mullerian ducts as well as the urogenital sinus. The paired Mullerian ducts originate in the fifth week as longitudinal grooves in the urogenital ridge, lying lateral to the mesonephric (Wolffian) ducts. The ducts grow caudally by cellular proliferation as solid tubes which canalize as they elongate. Caudally, these cross to the midline in front of (ventral to) the mesonephric ducts. The Mullerian ducts approach, fuse with each other, forming the uterovaginal canal, and join with the urogenital sinus in the seventh week (Fig. 1.1a) [2]. The proximal vertical portions of the ducts develop into the Fallopian tubes, retaining their funnel-shaped opening into the coelomic cavity at their origin as their fimbrial ends. The caudal fused portion gives rise to the uterine corpus and isthmus. The junction of the Mullerian duct with the urogenital sinus is the site of a solid mass of cells known as the Mullerian tubercle. The growth and canalization of this structure produces the cervix, upper vagina, and vaginal fornices (Fig. 1.1b) [3, 4].

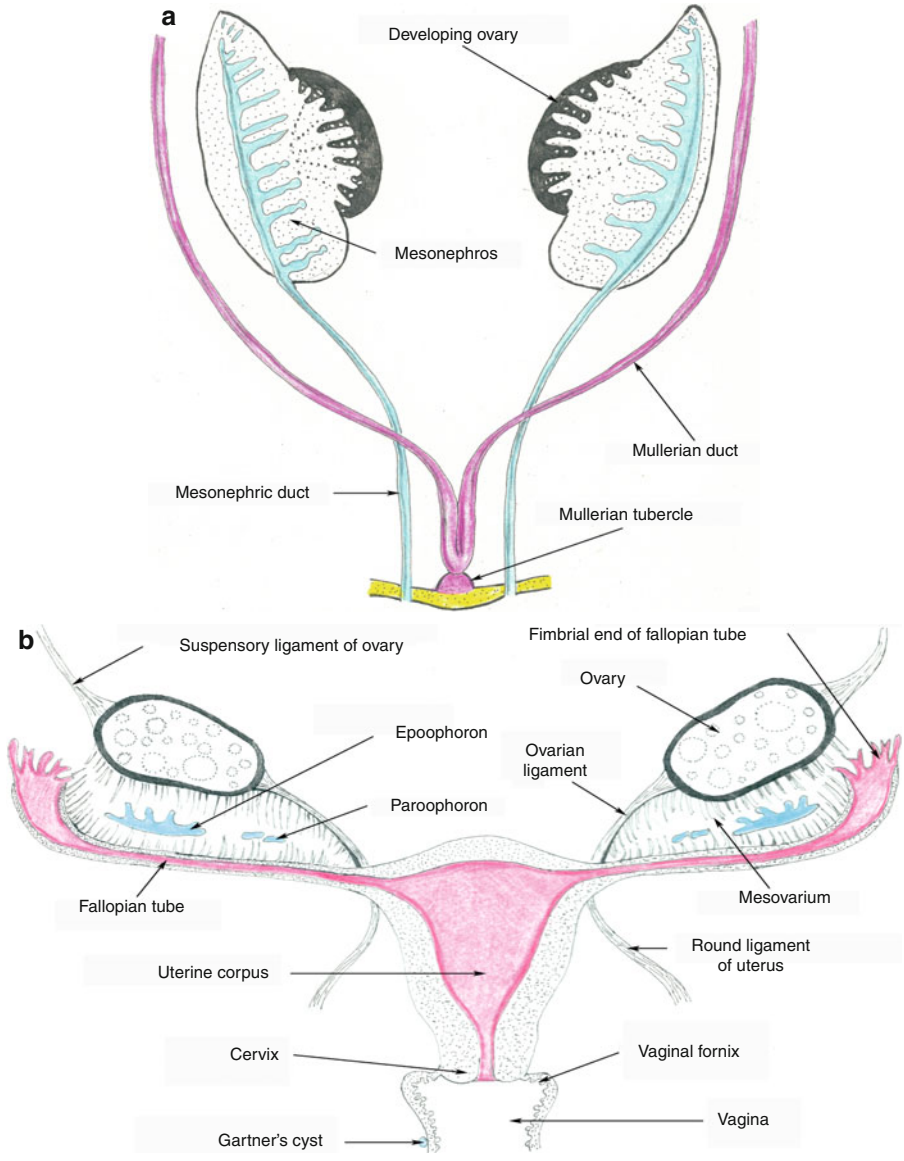

Fig. 1.1 (**a**) Mullerian and paramesonephric duct development. (**b**) The female genital tract fully developed with remnants of the mesonephric ducts in *blue*

Around day 66, there is an upward migration of squamous epithelial cells from the urogenital sinus. This structure, initially a solid cylinder of cells which later canalizes, is known as the vaginal plate and is unique to the human embryo [5]. Proliferation at the cranial end of the vaginal plate results in elongation of this outgrowth which becomes fully canalized by the fifth month. The caudal end of this plate is the site of the hymen. The vagina therefore has a dual origin with the upper portion, including the vaginal fornices, arising from the paramesonephric ducts and the lower portion from the urogenital sinus (Figs. 1.2, 1.3, 1.4).

More proximally endocervical mucinous glands appear between the 13th and 15th weeks together with differentiation of endometrial and serous epithelia in the upper genital tract. The development of the mesoderm surrounding the female genital tract in humans is incompletely understood, but experimental studies demonstrate that complex stromal epithelial interactions are crucial for site-specific epithelial differentiation [6]. The mesoderm consists of two layers. The inner layer forms the endometrium and endocervical stroma, tapering distally and possibly extending into the vagina and vulva. It is this inner layer of mesenchyme that is believed to induce tubal,

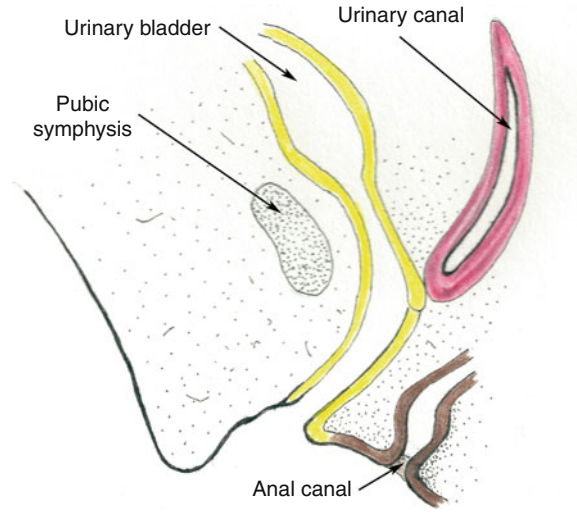

Fig. 1.2 Sagittal section through the developing uterovaginal canal at 9 weeks showing the Mullerian tubercle of paramesonephric and vaginal plate of urogenital sinus origin

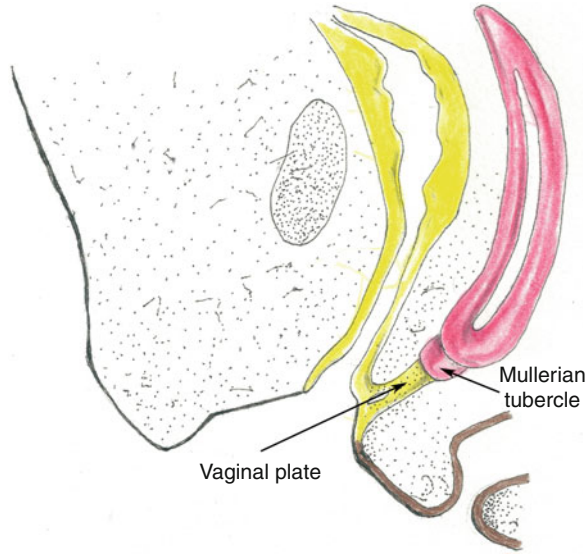

Fig. 1.3 The vagina at the end of the third month

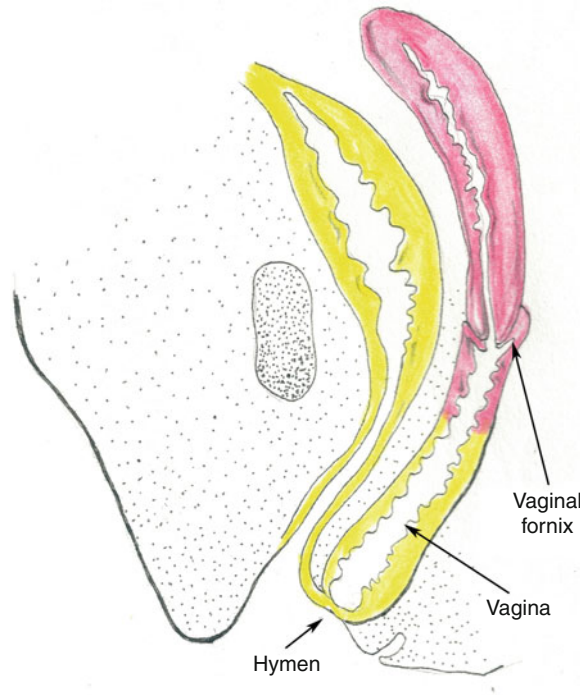

Fig. 1.4 The fully canalized vagina in the newborn female

endometrial, and endocervical types of glandular epithelial development [7]. The outer layer forms the muscle wall of the Fallopian tube, the myometrium, the outer cervical stroma, and the muscle wall of the vagina.

Development of external genitalia occurs under the influence of sex hormones [8]. In the fourth week, the cloaca begins to divide into the rectum dorsally and the urogenital sinus ventrally. By the sixth week, the urorectal membrane, a layer of mesoderm dividing the cloaca in a coronal plane, fuses with the cloacal membrane demarcating the urogenital sinus anteriorly and the anal canal posteriorly (Fig. 1.5a). Proliferation of the mesoderm and ectoderm lateral and ventral to the cloaca results in the formation of a pair of ectodermal elevations which are fused ventrally forming the genital tubercle and form two pairs of parallel ridges laterally. The medial pair is termed the urogenital folds, while the lateral pair are the labioscrotal folds (Fig. 1.5b). The genital tubercle, urogenital folds and labioscrotal folds give rise to the clitoris, labia minora and labia majora, respectively (Fig. 1.5c). The ventral portions of the labioscrotal folds fuse medially to produce the mons pubis. The labioscrotal folds fuse posteriorly within the urogenital membrane anterior to the anus.

The area bounded by the vaginal orifice and the urogenital sinus enlarges to form the vestibule (see below), which is therefore largely of endodermal origin apart from a variable area anterior to the urethra. This is morphologically and functionally distinct from the rest of vulval tissues which are mesodermally and ectodermally derived, reflected in differences in responses to sex hormones and other stimuli. Typically, irritation in endodermally derived areas is perceived as burning in contrast to the itching felt in ectodermal epithelia.

Anatomy and Histology of the Vagina

The vagina is an anteroposteriorly collapsed hollow fibromuscular tube about 9 cm in length in the adult female. This opens into the vulva inferiorly. Superiorly, the vagina communicates with the cervix. The axis of the vagina lies in an oblique line with the top of the vagina lying superior and posterior to the introitus. The axis of the

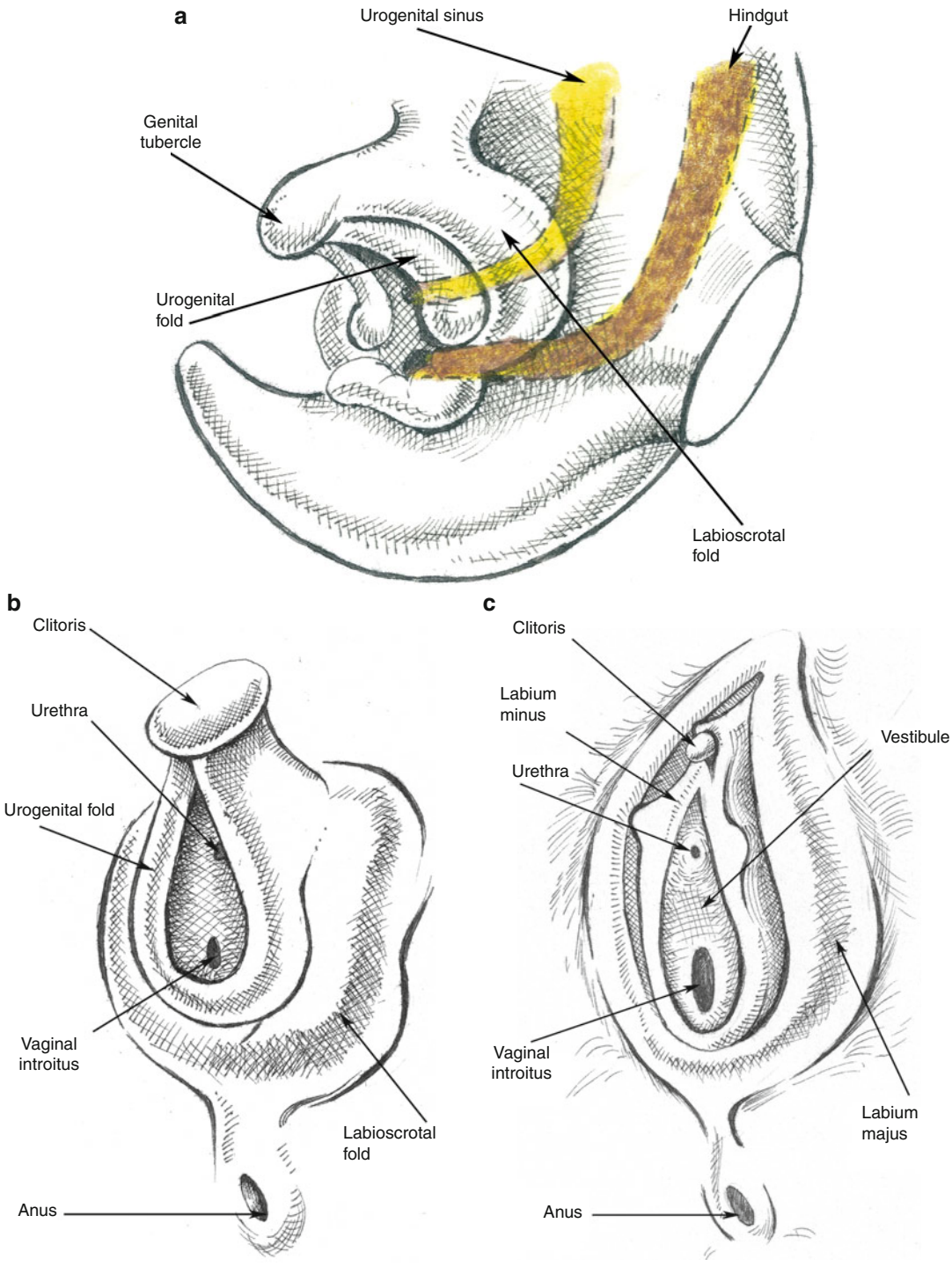

Fig. 1.5 (**a**) Development of the external genitalia begins with the appearance of the genital tubercle, labioscrotal fold, and urogenital fold; the cloaca has divided into the urogenital sinus and the hindgut. (**b**) The labioscrotal and urogenital folds remain separate in the female, enclosing the vestibule which receives the openings of the urethra and vagina (in the male, these pairs of folds fuse to form the scrotum). (**c**) The genital tubercle, urogenital folds, and labioscrotal folds give rise to the clitoris, labia minora, and labia majora, respectively

normally anteverted uterus and cervix forms an obtuse angle with that of the vagina, such that the external os of the cervix faces the posterior vaginal wall. The cervix bulges into the upper vagina and the blind folds of vaginal mucosa that surround the cervix are known as the fornices, being deepest posteriorly.

The inner surface of vagina is covered by a dull lining that bears many horizontal folds or rugae to enable stretching. There are normally no glands in the vagina and the secretions that are seen as part of the arousal response appear to be derived from transudate resulting from increased blood flow in mural vessels, with contributions from Bartholin's, sebaceous, sweat, Skene's, and endocervical glands [9, 10]. The vaginal fluid has a slightly acidic pH which varies with the phase of the menstrual cycle and during the arousal response when it has a higher pH and is rich in enzymes and immunoglobulins. The vaginal wall becomes more soft and relaxed during pregnancy and parturition.

The structures anterior to the vagina are the base of the urinary bladder and the urethra. The distal 2/3rds of the urethra is closely apposed to the anterior vaginal wall, separated only by a dense fused fascial layer. Posteriorly, the upper 1/4th of the vagina wall, including the posterior fornix, forms the anterior boundary of the cul-de-sac in the pelvic peritoneal cavity known as the pouch of Douglas which represents the deepest part of the peritoneal cavity. The distal part of the posterior wall of the vagina is separated from the rectum by the rectovaginal septum. The distal part of the posterior wall lies in relation to the perineal body and anorectal sphincters, separating the vagina from the anal canal. The most significant lateral relations are the ureters, which pass forward to enter the urinary bladder crossing beneath the uterine arteries just above the lateral fornices. The remaining lateral relations are the muscles that support the pelvic structures and form the pelvic floor, with the caudal most being the bulbocavernosus, which forms a sphincter around the distal vagina.

The vagina receives a richly anastomotic blood supply from the uterine, vaginal, middle rectal, and internal pudendal branches of the internal iliac arteries. Venous drainage is into a vascular plexus following the arterial supply and draining ultimately via the internal iliac vein.

Lymphatic drainage of the vagina is complex. Broadly, the superior and anterior portion follows the uterine artery and drains into the external iliac lymph nodes. The posterior vagina drains into inferior gluteal, sacral, and anorectal lymph nodes. The distal vagina, like the vulva, drains into inguinofemoral lymph nodes. Rich anastomosis, however, means that any part of the vagina may drain into any of these three nodal sites: pelvic, anorectal, or inguinofemoral [10].

Four layers are seen on histological examination of the vaginal wall [9]. The surface epithelium is of nonkeratinizing stratified squamous type. This consists of basal, parabasal, intermediate, and superficial squamous cells, identical to the layers of the ectocervix and similarly responsive to hormonal stimuli. Thus, the thickness and maturation of the epithelium varies with age and menstrual phase. Basal cells are cuboidal with uniformly hyperchromatic nuclei and high nuclear to cytoplasmic ratio. Parabasal cells form a layer that is 2–5 cells thick. These cells are polygonal with round dark nuclei and show mitotic activity. As maturation proceeds, the cells become larger and flatter and the nuclei progressively smaller. Loss of maturation occurs after the menopause and in other low estrogen states. The intermediate and superficial epithelial cells are glycogenated. Breakdown of glycogen by lactobacilli normally resident in the adult vagina contributes to the protective acidic pH through production of lactic acid. Glycogenation imparts a perinuclear clear zone resulting in a resemblance to koilocytosis which should only be diagnosed in the presence of abnormal nuclear features.

The epithelium rests on a variably distinct lamina propria composed of a loose fibrovascular stroma with collagen and elastic tissue. There may be occasional stellate and multinucleated cells present in this layer (see Chap. 8). The major portion of the thickness of the vaginal wall is formed by the dense fibromuscular layer. The smooth muscle is poorly demarcated into inner circular and outer longitudinal layers which

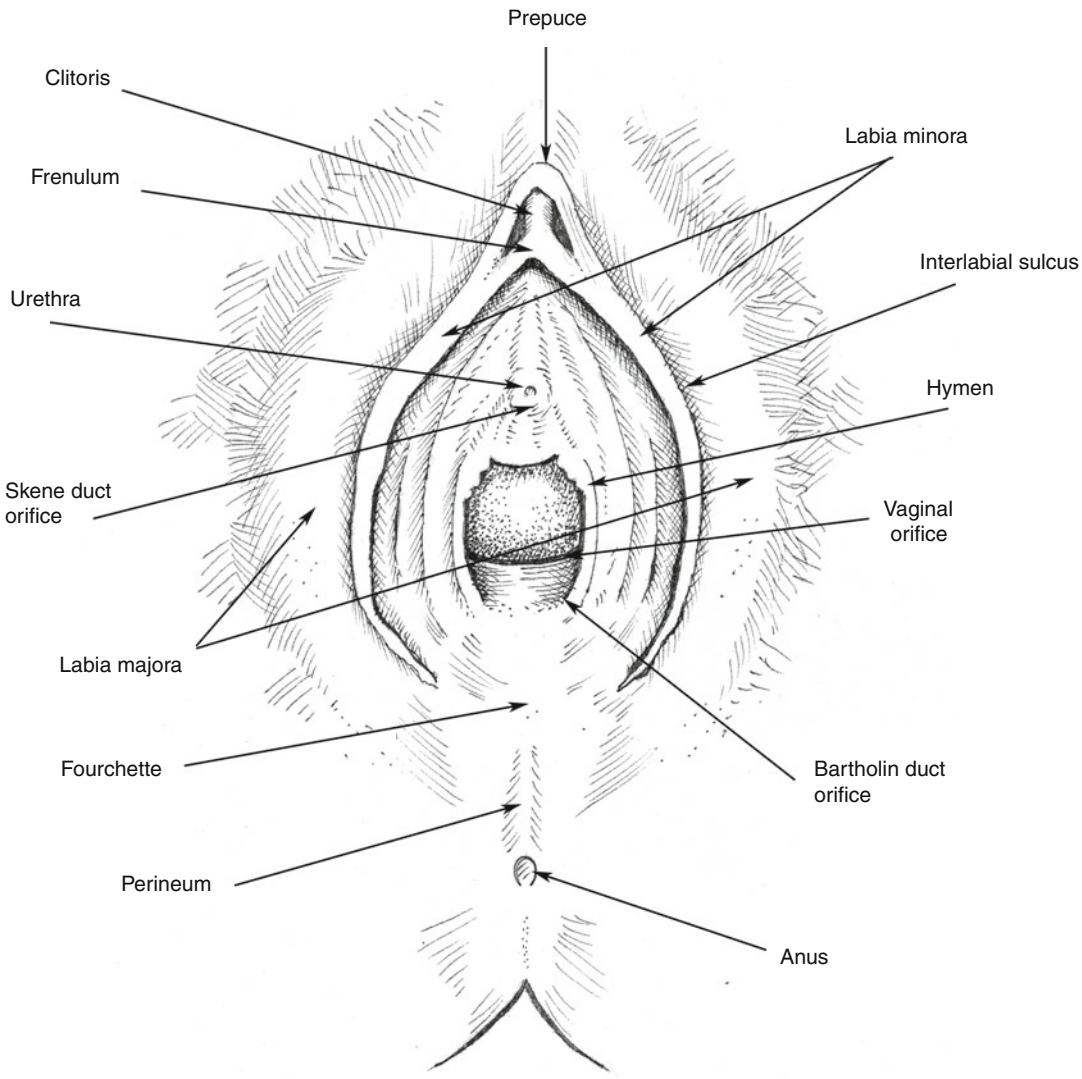

Fig. 1.6 The external adult genitalia showing the clitoris with prepuce and frenulum, paired outer lips—the labia majora, paired inner lips—the labia minora, medial urethra, vaginal introitus, and fourchette. A pair of Skene's glands opens in to the anterior vestibule and paired Bartholin's glands into the posterior vestibule. The perineum and anus lie posteriorly

merge with adjacent pelvic muscles. An adventitial fibroadipose layer lies outermost.

Remnants of the mesonephric ducts or Gartner's duct may be seen in the vaginal wall usually in a lateral position though rarely elsewhere (Fig. 1.1b) [11]. These consist of a ductal structure surrounded by smooth muscle and variable numbers of glands. The glands are lined by non-ciliated and non-mucinous cells with a high nuclear to cytoplasmic ratio, scanty pale or clear cytoplasm, and bland nuclei. The luminal spaces characteristically contain eosinophilic material.

Anatomy and Histology of the Vulva

The vulva constitutes the external genitalia of the human female (Fig. 1.6). Anteriorly, including and bounded by the mons pubis, the vulva lies between the inguinogluteal folds laterally and the

anus posteriorly. Structures included in the vulva are the mons pubis and labia majora, labia minora, clitoris, and vestibule, the last containing the vaginal introitus and urethra as well as openings of the major vestibular (Bartholin's), periurethral (Skene's), and minor vestibular glands. The proximal boundary at the vaginal introitus is the hymen, the inferior surface of which forms the roof of the vestibule. An imaginary line, the vestibular line of Hart, demarcates the vestibule, of endodermal (urogenital sinus) origin from the rest of the vulva which is ectodermal in origin [9]. Functionally and histologically, this line demarcates sebaceous gland-bearing skin of the medial labia majora from the hormone sensitive and glycogenated nonkeratinized stratified squamous epithelium of the labia minora and vestibular structures. The line is formed by the prepuce anteriorly, the labia minora laterally, and posteriorly by the perineal body, a poorly defined fibromuscular node midway between the two ischial tuberosities where the muscles of the pelvic floor converge [12].

The mons pubis and labia majora consist of skin, subcutaneous fat, and some smooth muscle. The labia majora are bounded medially by the interlabial sulcus and posteriorly by the perineal body. At the onset of puberty, coarse, short, and curly pubic hair appears over the mons pubis and lateral surface of the labia majora. The medial surface of the labia majora is devoid of hair, and sebaceous and apocrine glands open directly onto the skin surface. These may be visible to the naked eye as small, white Fordyce spots. The histology of the skin covering these structures is identical to that elsewhere over the body [9, 13].

The labia minora are folds of nonkeratinizing stratified squamous epithelium and subepithelial connective tissue that includes richly vascular erectile tissue and elastic fibers. These folds are devoid of adipose tissue, hair, and sebaceous glands except close to the interlabial sulcus and on their posterolateral aspects. Anteriorly, each labium minus forks to contribute to the prepuce anterior and the frenulum posterior to the clitoris.

The clitoris is an erectile structure formed, like the penile shaft, of two columns of incompletely demarcated erectile tissue, the corpora cavernosa. These have richly innervated fibrous sheaths. The surface is covered by keratinized stratified squamous epithelium. There are no glands. The prepuce forms a fold over the clitoris and consists of keratinized stratified squamous epithelium and fibrovascular stroma. Posteriorly, the clitoris is bounded by the frenulum, the junction of the labia minora. The corpus spongiosum is divided in the female into bilateral vestibular bodies composed of erectile connective tissue, lying deep within the vestibule, lateral to the vaginal orifice [2].

The vestibule is covered by glycogenated nonkeratinized stratified squamous epithelium resting on loose connective tissue with variable amounts of erectile tissue included. This epithelium merges with transitional lining of the urethra and ductal epithelia of the major (Bartholin's) and minor vestibular glands as well as the periurethral (Skene's) glands. The vestibule of the vulva corresponds to the male urethra where this area is absorbed within the penile shaft.

The urethral meatus is a 0.1–1 mm opening with slightly rolled edge, directly anterior to the vaginal orifice and about 2.5 cm posterior to the clitoris. This is covered by nonkeratinizing stratified squamous epithelium, which merges with transitional mucosa at a variable distance within the urethra, an anteroposteriorly collapsed tubular structure measuring about 4 cm in length and 6 mm in diameter in adult females [2].

The vaginal introitus is the inferior opening of the vagina, marked by the hymen. The apposed anterior and posterior walls of the vagina make this a closed structure requiring insertion of a speculum to separate the walls during examination. The hymen is an incomplete membrane present at the introitus. This may range from being an indistinct rim to being annular, cribriform, or imperforate. The hymen may be torn by coitus, instrumentation, or use of tampons. Following parturition, the remnants of the hymen may appear as tags—the carunculae myrtiformes. The hymen consists of glycogenated nonkeratinizing stratified squamous epithelium with scant fibrovascular stroma.

The periurethral Skene's glands are paired structures about 1.5-cm maximum dimension that are analogous to the male prostate. These mucinous glands have openings directly into the vestibule posterior and lateral to the urethra as well as within the distal posterolateral urethra. The glands are lined by pseudostratified mucin-secreting columnar epithelium and the ducts by transitional epithelium, merging with vestibular squamous epithelium close to their orifices [13].

The major vestibular or Bartholin's glands are paired branching tubuloalveolar mucinous glands that lie in the posterolateral aspect of the vulva deep to the labia majora, labia minora, and posterior part of the hymen. These correspond to the bulbourethral or Cowper's glands in the male. The glands are composed of acini lined by simple mucin-secreting columnar epithelium. Each gland opens through a single Bartholin's duct which measures about 2.5 cm in length. The ducts are lined by mucinous epithelium close to the acini, changing to transitional epithelium and distally merging with squamous epithelium. The gland openings are situated in the posterolateral part of the vestibule, inferior to the hymen. Additional minor vestibular glands are simpler superficial tubular mucinous glands within the subepithelial stroma that open directly onto the vestibular surface. These are analogous to the urethral Littre glands in the male. These glands and their ducts show a variable degree of squamous metaplasia and occasionally become completely replaced by squamous epithelium.

Additional anogenital glands are present within the interlabial sulcus. These are similar morphologically and immunohistochemically to mammary glands and may consist of simple or more complex lobular units opening into a duct [14]. The structures are surrounded by a variably fibrotic stroma and lined by a dual layer of luminal cuboidal to columnar layer resting on a myoepithelial layer. The luminal cells are of apocrine type, but a milk line of vestigial mammary glands does not exist in humans (see Chap. 9) [15].

The fourchette is the posterior portion of the vestibule marked by the junction of the labia minora. The union of the labia majora is indistinct posteriorly and the 2.5–3 cm area between this and the anus forms the gynecological perineum. Deep to this lies the perineal body composed of the junction of the anal sphincter, bulbocavernosus, and superficial perineal muscles of the pelvic floor [2, 12].

Blood supply to the vulva is derived from the femoral artery, via superficial and deep external pudendals, and internal iliac artery, via the internal pudendal [9, 13]. These give rise to the anterior and posterior labial vessels. The clitoris, including its erectile apparatus, is supplied through a separate anterior clitoral artery. The vestibule derives its supply from the anterior vaginal artery. Venous drainage follows the arterial supply.

The lymphatic drainage of the vulva is to the superficial inguinal and femoral lymph nodes [9, 13]. Drainage is ipsilateral though the clitoris and midline perineal structures drain bilaterally. The lymphatics course anteriorly and superiorly from the more medial structures and proceed laterally with channels from the labia majora to enter the femoral and inguinal lymph nodes. The superficial inguinal lymph nodes are divided into two groups by the ligament of Poupart. The superior group is situated above the ligament and the inferior between the ligament and the junction of saphenous vein and fascia lata.

Disorders of Development

Developmental Abnormalities of the Vagina

Imperforate Hymen and Transverse Vaginal Septum

Imperforate hymen is a rare abnormality in which the vaginal orifice is covered completely by a membrane composed of fibrovascular stroma covered by stratified squamous epithelium. The condition, estimated to occur in about 1/1,000 females [16], may be diagnosed at birth as a result of a bulge due to collected mucus. Usually, the diagnosis is made at puberty, when hematocolpos results from

collected menstrual blood. If long-standing, this can be complicated by retrograde passage of menstrual products into the pelvic cavity leading to adhesion formation, endometriosis, and infertility [11].

A more severe abnormality is the presence of a transverse vaginal septum [11]. This may be complete or incomplete and seen at any level of the vagina. The inferior portion of the canal may be fully developed and lined by normal nonkeratinizing stratified squamous epithelium. The upper surface is lined by glandular epithelium, reflecting the dual origin of the vagina and the need for communication between the Mullerian and urogenital sinus-derived portions for its normal development. Complete septa may result in complications due to retrograde menstruation.

Septate Vagina

Septate vagina is rare and usually associated with severely abnormal uterine development in the form of a duplicated uterus and cervix [16].

Other Vaginal Developmental Disorders

Vaginal adenosis refers to persistence of glandular epithelium in the vagina. This is seen frequently, but not invariably, in women exposed to diethylstilbestrol (DES) in utero [16]. The glandular epithelium is usually mucinous but can also be tuboendometrial, especially in cases following exposure to DES in the vagina. The underlying defect in such cases is hypothesized to be a failure of normal segregation of the inner layer of mesenchyme, which induces the development of mucinous and tuboendometrial epithelium and failure of normal upgrowth of the urogenital sinus that appears to be necessary for limiting this differentiation to the upper female genital tract [4]. Vaginal adenosis is probably the developmental disorder of greatest importance to the gynecological pathologist, and its diagnosis is dealt with in the chapter on glandular abnormalities (see Chap. 4).

Congenital opening of the urethra or the anus into the vagina occurs due to abnormal cloacal development. In its most severe form, there may be retention of a common cloacal opening communicating with the rectum, uterus, and urinary bladder [16].

Developmental Abnormalities of the Vulva

Ambiguous genital development is rare and may occur with virilizing syndromes or various forms of hermaphroditism [13]. This manifests as clitoral hypertrophy and a variable degree of labial fusion. Congenital asymmetry of the vulva due to hypogenesis or hypertrophy is also rarely reported.

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Vulvovaginal Infections

2

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Abstract

Vulvovaginal infective diseases encompass a spectrum of primary and secondary bacterial, viral, fungal, and parasitic, including protozoal, infections that variably affect females of different age groups and in varying global, geographic locations. In addition, the disease spectrum is also influenced by the underlying immune status of the patients. The primary vulvovaginal infections are dominated by the sexually transmitted diseases that are grouped under the rubric "genital ulcer disease" and encompass syphilis, chancroid, donovanosis, lymphogranuloma venereum, and herpes simplex virus infection. Syndromic medical management of genital ulcer disease has not only decreased the need for diagnostic biopsies but has also limited the exposure of pathologists to the wide range of histopathological features, mimicry, and pitfalls of these ulcerative entities and the associated diagnostic challenges. Hence, familiarity with the spectrum of features that characterize the disease is critical to avoid misdiagnosis of other inflammatory disease mimickers. The histopathological diagnosis of vulvovaginal involvement by systemic infections is plagued by clinical underrecognition of vulvovaginal involvement by systemic infections and the attendant-altered clinicopathological morphology because of exposure of the vulvovaginal area to friction, moisture, and pruritus. The biopsy therefore plays a pivotal diagnostic role in the confirmation of an increasing range of infections, including those that are unsuspected clinically.

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Introduction

A spectrum of primary and secondary infective processes may involve the vulvovaginal area. While some of these infections represent primary genital tract infections, other vulvovaginal infections are acquired, either by contiguous spread from adjacent organs or as part of system dissemination. The primary vulval infections are

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dominated by sexually transmitted diseases that are grouped under the rubric "genital ulcer disease." While the vulvovaginal manifestations of systemic infections may share phenotypic features of the diseases in extravulvovaginal locations, the exposure of the vulvovaginal area to friction, moisture, and pruritus may alter the morphological diagnostic features. The clinical phenotype of vulval infections overlaps with those of noninfective vulval dermatoses, posing clinical diagnostic challenges. Vulvovaginal infections may be assessed, for the first time, by a spectrum of health-care professionals including family practitioners, venereologists, dermatologists, gynecologists, or infectious disease specialists. Hence, clinical suspicion of vulvovaginal infections varies as no single practitioner oversees the spectrum of diseases. The biopsy may therefore be pivotal in the diagnostic confirmation of many vulvovaginal infections, including those that are not suspected clinically.

Predominantly Primary Vulvovaginal Infections

Genital Ulcer Disease

Syphilis

Syphilis, caused by *Treponema pallidum*, is a predominant sexually transmitted infectious disease of worldwide distribution [1]. Congenital and acquired forms of syphilis are characterized by cutaneous involvement, including vulval manifestations [2]. Acquired syphilis is divided into primary, secondary, latent, and tertiary stages [3]. *Clinical features*: The manifestations of primary syphilis occur 10–90 days postinfection as a painless "chancre" at the site of inoculation in association with local lymphadenopathy [3]. Rarely, more than one chancre may be present. Although resolution of the chancre occurs, vascular invasion facilitates the secondary stage, 2–6 months later [3]. In addition to mucocutaneous lesions, visceral and constitutional symptoms occur. The cutaneous clinical phenotype of secondary syphilis is heterogeneous and includes maculopapular, annular, psoriasiform, lichenoid, pustular, and ulcerative lesions [4]. In flexural and anogenital skin, fleshy verrucous papules referred to as "condylomata lata" may be present. Tertiary syphilis occurs many years after disease onset but this may be accelerated in the setting of HIV infection [5, 6]. Cutaneous lesions, described in 70% of patients, include nodular tertiary and benign gummatous syphilis. Classical serologic testing for syphilis encompasses nontreponemal (rapid plasma reagin or Venereal Disease Research Laboratory) and treponemal tests (*T. pallidum* hemagglutination assay or *T. pallidum* particle agglutination) [7]. These tests may be negative in primary syphilis, and the serological tests are limited by low sensitivity and specificity [8].

Interactions between HIV and *T. pallidum* cause an accelerated disease course of both infections, altered clinical and laboratory profiles, increased risk for complications, and a decreased response to antisyphilitic treatment [9–11]. Serological confirmation of syphilis in HIV-infected patients may be hampered by an increased rate of negative serological tests in primary and secondary syphilis, increased false-negative nontreponemal antibody tests due to the prozone phenomenon [12], failure to clear nontreponemal antibody after treatment, and seroreversion of specific treponemal antibody tests to a negative state after treatment [13]. The accelerated cutaneous syphilitic lesions manifest as lues maligna with severe cutaneous ulceration and pseudolymphomatous mycoses-fungoides like lesions [14, 15]. The curative treatment schedule should include higher doses of penicillin [16, 17].

Microscopic features: *Primary syphilis* (*chancre*): The initial microscopic features of primary syphilitic encompass endothelial swelling and proliferation and an associated superficial and deep perivascular mononuclear inflammatory cell infiltrate. There is subsequent luminal occlusion as a result of endothelial hyperplasia and endarteritis obliterans and increased density of the mononuclear inflammatory cell in infiltrate, variable ulceration, and associated pseudoepitheliomatous hyperplasia. *Secondary syphilis*: Two main reactional patterns characterize secondary syphilis: psoriasiform (Fig. 2.1a, b) and lichenoid (Fig. 2.2a) [9]. The psoriasiform pattern (Fig. 2.1a,

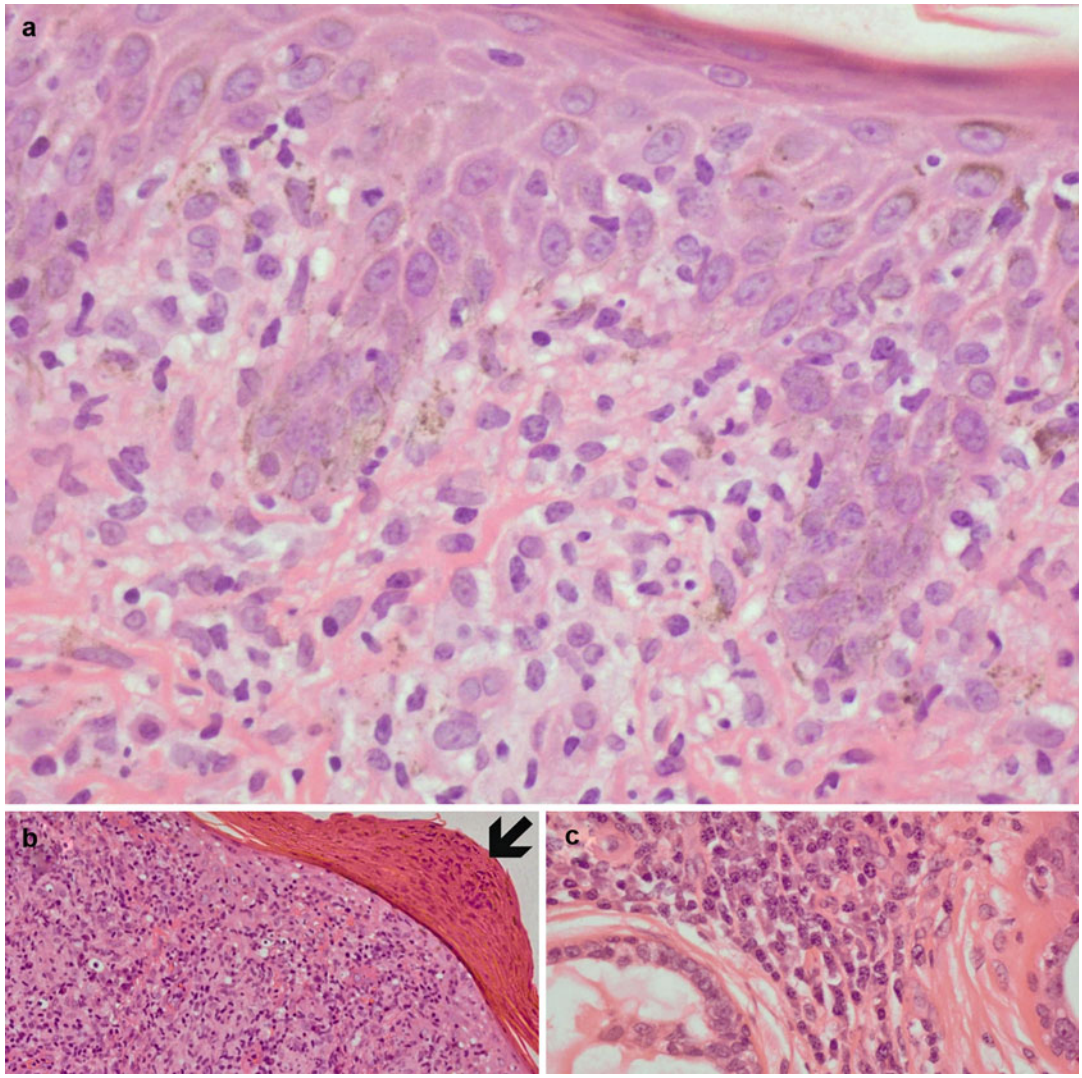

Fig. 2.1 Secondary syphilis: psoriasiform epidermal hyperplasia (**a**) with confluent parakeratotic crust (**b**, *arrow*) and plasma cells within eccrine secretory coil (**c**)

b) demonstrates epidermal acanthosis and club-shaped elongation of the rete ridges while the lichenoid pattern is typified by a band-like interface inflammatory infiltrate (Fig. 2.2a). The epidermis also demonstrates variable parakeratosis, apoptosis, erythrocyte extravasation, and transepidermal neutrophils and eosinophils (Figs. 2.1a, b and 2.2a, b). The dermal inflammatory cell infiltrate, composed mainly of $CD8^+$ T lymphocytes, plasma cells, and macrophages, may extend deep into the dermis in perivascular and periappendageal locations (Fig. 2.1c) [18]. Other variable findings include the presence of nonnecrotizing granulomas (more common in older lesions) and neutrophilic eccrine hidradenitis and the absence of plasma cells. Condylomata lata demonstrate more pronounced epidermal hyperplasia and intraepidermal microabscesses [19]. Lues maligna is characterized by thrombotic endarteritis obliterans (Fig. 2.2c), most pronounced at the dermal-subcutaneous junction, cutaneous infarction, ischemic ulceration, and a dense plasmacytic and histiocytic infiltrate. Pustular syphilis is characterized by folliculocentric

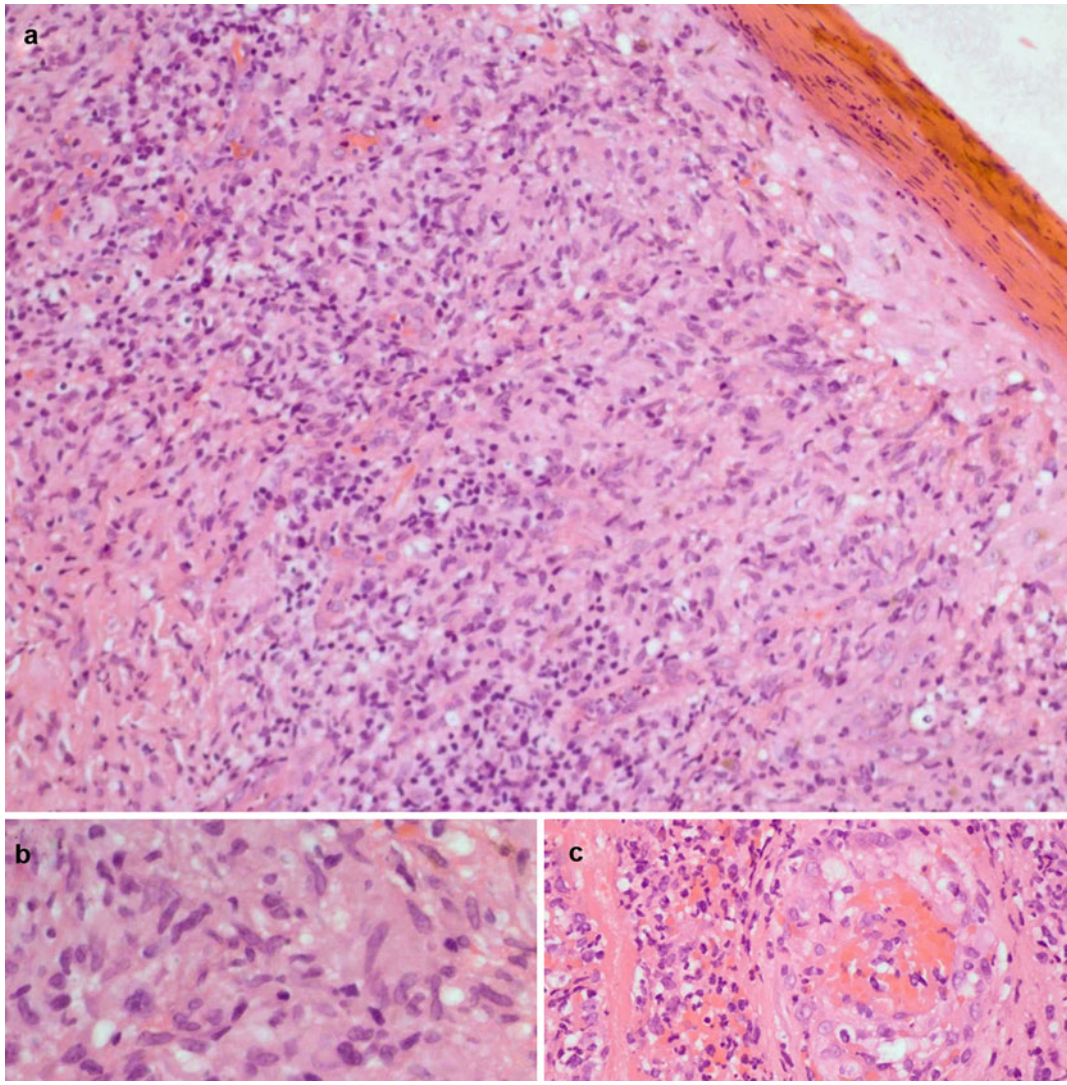

Fig. 2.2 Secondary syphilis: lichenoid inflammatory reaction pattern (**a**) with granulomatous inflammation (**b**). Thrombotic vasculitis in lues maligna (**c**)

suppurative inflammation and a surrounding perivascular lymphoplasmacytic infiltrate. Spirochetes are easily identified on silver stains. *Tertiary syphilis*: nodular tertiary syphilis is characterized by a dermal and subcutaneous perivascular plasmacytic infiltrate, variable granulomatous inflammation, and endarteritis obliterans (Fig. 2.3a). Benign gummatous syphilis is characterized by necrotizing granulomatous inflammation in which broad, irregular, acellular debris is surrounded by epithelioid histiocytes, multinucleate giant cells of Langhans type, lymphocytes, plasma cells, and fibroblasts (Fig. 2.3b).

Traditionally, *T. pallidum* has been identified using silver-impregnation staining, including Warthin Starry, Steiner, and Levaditi stains (Fig. 2.3c) [20]. The introduction of direct and indirect immunofluorescence and immunohistochemical spirochetal detection methods on fresh or archival wax block tissue has decreased the diagnostic challenges associated with nonspecific artefactual arygyrophilia of cutaneous elements, including melanin pigment and connective tissue elements [20–22]. While spirochetes are demonstrated in primary and secondary, and to a lesser extent, tertiary, syphilis, significantly different