Benign Diseases of the Cervix

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Thomas C. Wright and Brigitte M. Ronnett

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T. C. Wright (✉)
Department of Pathology and Cell Biology, Columbia University, New York, NY, USA
e-mail: tcw1@columbia.edu

B. M. Ronnett
Department of Pathology, Division of Gynecologic Pathology, Johns Hopkins University School of Medicine, Baltimore, MD, USA
e-mail: bronnett@jhmi.edu

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This chapter begins with a brief review of the gross anatomy of the cervix including its blood supply and lymphatic drainage. It then discusses the normal histology and physiology of the cervix including a description of the immunohistochemical staining patterns of the different cell types. The size and configuration of the cervix, as well as the localization of specific types of epithelial cells on the mucosal surface and their degree of differentiation, change during a woman's lifetime. These changes play a fundamental role in the development of several pathological conditions including cervical cancer. An important anatomical landmark is the squamocolumnar junction (SCJ). This is the dividing line between the native squamous epithelium of the outer portion of the cervix and the mucus secreting columnar epithelium of the endocervical canal. The location of the SCJ migrates during a woman's lifetime. The SCJ is important because it contains specialized epithelial cells that appear to be the cell of origin of invasive squamous cell carcinomas. The majority of cervical precancers involve this region. Benign changes that occur in the cervical epithelium include metaplastic changes including squamous metaplasia, tubal metaplasia and transitional cell metaplasia, responses to high levels of hormones resulting in the Arias-Stella reaction and pseudodecidual reactions, inflammatory conditions and infections, as well as pseudoneoplastic glandular conditions. Pseudoneoplastic glandular lesions such as florid mesonephric hyperplasia and lobular endocervical glandular hyperplasia (LEGH) are particularly challenging since they are relatively uncommon and can be mistaken for endocervical adenocarcinoma. The chapter concludes with a description of a number of benign tumors, cysts, and tumor-like conditions that the practicing surgical pathologist can encounter.

Gross Anatomy

The uterus is divided into the corpus, isthmus, and cervix. The cervix (term taken from the Latin, meaning *neck*) is the most inferior portion of the uterus, protruding into the upper vagina. The transition between the endocervix and the lower portion of the uterine corpus is termed the *isthmus* or *lower uterine segment*. The latter is used for descriptive purposes during gestation and labor and is an important landmark for the pathologist when describing cancers of the uterine corpus. The muscular layer in the region of the isthmus is less well developed than in the corpus, a feature that facilitates effacement and dilation during labor. The vagina is fused circumferentially and obliquely to the distal part of the cervix and is divided into an upper, supervaginal, and lower vaginal portion. The cervix measures 2.5–3.0 cm in length in the adult nulligravida, and when normally positioned is angled slightly downward and backward. The vaginal portion (portio vaginalis) of the cervix, also referred to as the *exocervix*, is delimited by the anterior and posterior vaginal fornices; it has a convex elliptical surface. The portio may be divided into anterior and posterior lips, of which the anterior is shorter. In the center of the exocervix is the external os. The external os is circular in the nulligravida and slit-like in the parous woman (Fig. 1a, b). The external os is connected to the isthmus of the cervical canal (endocervix). The canal is an elliptical cavity, measuring 8 mm in its greatest diameter and contains longitudinal mucosal ridges, the plicae palmatae.

The blood supply of the cervix is provided by the descending branches of the uterine arteries, reaching the lateral walls along the upper margin of the paracervical ligaments (cardinal ligaments of Mackenrodt) (Fig. 2). These ligaments and the uterosacral ligaments, which attach the supervaginal portion of the cervix to the second through fourth sacral vertebrae, are the main sources of fixation, support, and suspension of the organ. The venous drainage parallels the arterial system, with communication between the cervical plexus and neck of the urinary bladder. The lymphatics of the cervix have a dual origin: coursing beneath the mucosa and deep in the fibrous stroma. Both systems collect into two lateral plexuses in the region of the isthmus and give origin to four efferent channels running toward the external iliac and obturator lymph nodes, the hypogastric and common iliac nodes, the sacral nodes, and the nodes of the posterior wall of the urinary bladder (Fig. 2). The innervation of the cervix is chiefly limited to the endocervix and peripheral deep portion of the exocervix. This distribution is responsible for the relative insensitivity to pain

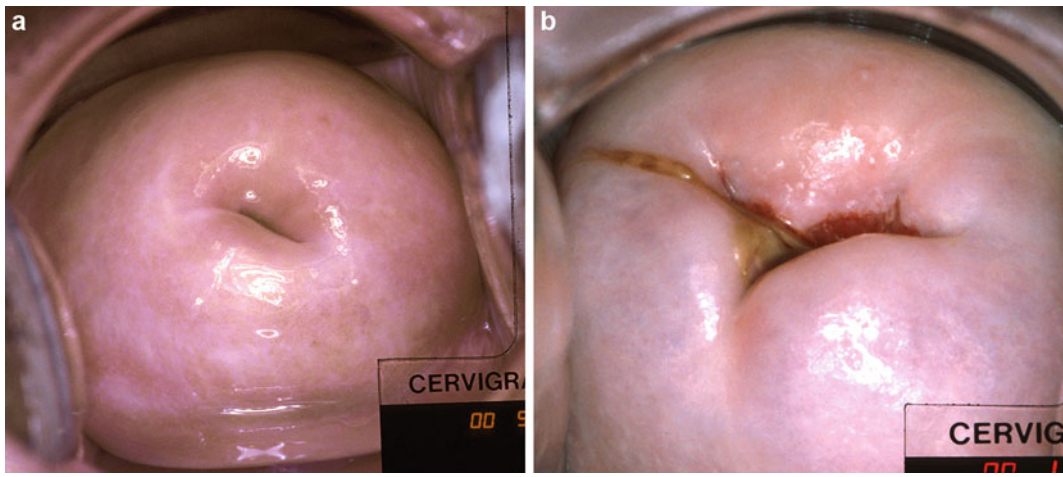

Fig. 1 Normal cervix uteri. *Left:* Nulliparous cervix with a circular external os. *Right:* Parous cervix with a slit-like external os

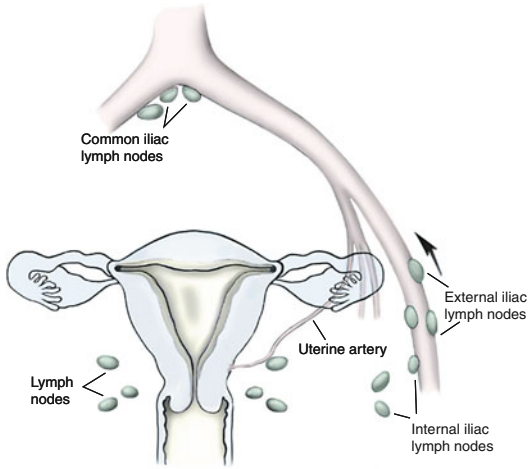

Fig. 2 Anatomy of the cervix. The blood supply and lymphatic drainage of the cervix are demonstrated

of the inner two-thirds of the portio vaginalis. The cervical nerves are derived from the pelvic autonomic system, the superior, middle, and inferior hypogastric plexuses.

Histology and Physiology

The cervix is composed of an admixture of fibrous, muscular, and elastic tissue and is lined by columnar and squamous epithelium. Fibrous connective tissue is the predominant component. Smooth muscle comprises 15% of the substance and is located mainly in the endocervix, the portio vaginalis being nearly devoid of smooth muscle fibers. In contrast, at the isthmus, 50–60% of the supportive tissue consists of concentrically arranged smooth muscle which acts as a sphincter.

Squamous Epithelium

Histology

The mature nonkeratinized squamous epithelium of the exocervix is similar to the vaginal epithelium but under normal circumstances lacks the rete pegs seen in the vagina. It is divided into three zones: the basal/parabasal or germinal cell layer, which is responsible for continuous epithelial renewal, the midzone or stratum spinosum, the dominant portion

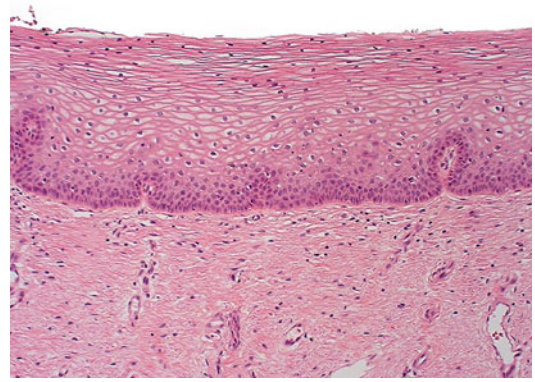

Fig. 3 Normal squamous epithelium. The mature squamous epithelium of the portio of the cervix shows a gradual ascending maturation, vacuolization of midzone cells, and a single layer of basal cells in which the nuclei are perpendicularly oriented to the basal lamina. The stromal-epithelial junction contains a finger-like, fibrovascular stromal papilla penetrating the lower portion of the epithelium

of the epithelium, and the superficial zone, containing the most mature cell population (Fig. 3).

The basal/parabasal or germinal layer contains two types of cells. One type is the true *basal cell* which is about 10 μm in diameter, with scant cytoplasm and oval nuclei oriented perpendicularly to the underlying basal lamina (Fig. 4). The other type of cell is termed the *parabasal cell* because of its geographic placement. Parabasal cells are larger than basal cells and have more cytoplasm. Parabasal cells typically form a layer that is 1–2 cells thick over the basal layer.

Epithelial regeneration is the major function of the basal and parabasal layers. Accordingly, epidermal growth factor receptors including human epidermal growth factor receptor 2 (HER-2)/neu, and receptors for estrogen and progesterone are found predominantly in the basal and parabasal cells (Berchuck et al. 1990; Kanai et al. 1998). The number of growth factor receptors becomes reduced as the squamous epithelial cells differentiate into the intermediate cell layer. Basal cells appear to act as stem cells whereas parabasal cells comprise the actively replicating compartment. Indeed mitotic figures are usually found in parabasal but not basal cells and other markers for actively proliferating cells such as Ki-67 antigen, proliferating cell nuclear antigen (PCNA) and other cyclins are localized to

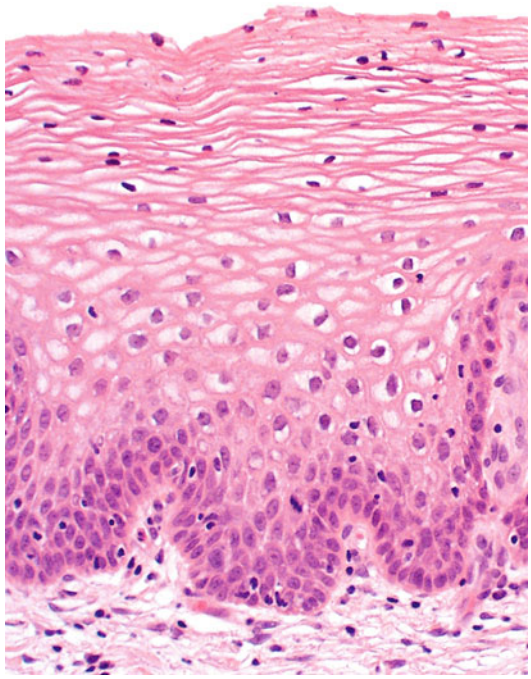

Fig. 4 Normal squamous epithelium. Under normal conditions, the basal layer acts as a reserve cell layer and mitoses are only identified in parabasal cells

parabasal cells (Table 1) (Konishi et al. 1991; Raju 1994; Cho et al. 1997).

The midzone is occupied by cells that are undergoing maturation, characterized by a gradual increase in the volume of the cytoplasm. Nuclear size, however, remains stable up to the most superficial cell level. These cells are referred to as *intermediate cells*. They do not divide. Intermediate cells have abundant periodic-acid Schiff (PAS)-positive, diatase-labile intracellular glycogen, which is responsible for the clear, vacuolated appearance of their cytoplasm.

The superficial zone forms the most differentiated compartment of the squamous epithelium. These cells are flattened and have a larger area of cytoplasm (50 μm in diameter) and smaller pyknotic nuclei than the underlying intermediate cells. The pink, eosinophilic cytoplasm has abundant intermediate filaments, which provide rigidity (Fig. 5). Superficial cells also contain occasional membrane-bound keratinosomes by electron microscopy.

The squamous epithelium of the portio is supported by fibrous connective tissue, devoid of endocervical glands. It has occasional finger-like extensions into the epithelium, the stromal papillae (Fig. 3). The penetrating vessels within the papillae supply the epithelial cells with nutrients and oxygen. Occasional free nerve endings are seen entering the stromal papilla.

In postmenopausal women, who no longer produce ovarian hormones, the squamous epithelium is atrophic with little or no intracytoplasmic glycogen (Fig. 6). Surface epithelial maturation and stromal papillae are absent. These cellular alterations should not be confused with cervical intraepithelial neoplasia. The atrophic epithelial covering does not adequately protect the subepithelial vasculature against trauma, a situation that frequently leads to bleeding and inflammation.

Effect of Estrogen and Progesterone

The epithelium of the exocervix is remodeled by proliferation, maturation, and desquamation during the reproductive period. The epithelium is completely replaced by a new population of cells every 4–5 days; the process of squamous epithelial maturation can be accelerated to 3 days by the administration of estrogenic compounds (Koss 1992). Estrogen receptors (ERs) have been localized to nuclei in the basal, parabasal, and intermediate cell layers (Kanai et al. 1998; Konishi et al. 1991). Compared to the endometrium, in the cervix only a small increase of ER levels occurs during the follicular phase as compared to the luteal phase. In atrophic and highly inflamed exocervical epithelium, the amount of ER is reduced. No, or only low levels, of progesterone receptors (PRs) are detected immunohistochemically in the exocervical epithelium during the follicular phase of the menstrual cycle, whereas during the luteal phase and during pregnancy, PRs appear in the parabasal cell layer (Konishi et al. 1991; Nikolaou et al. 2014). Both ER and PR can be detected in stromal fibroblasts of the exocervix throughout the menstrual cycle.

In general, estradiol-17ß stimulates epithelial proliferation, maturation, and desquamation,

Table 1 Immunohistochemical staining patterns of normal cervical tissues

Antibody	Cells of Stratified Squamous Epithelium				Reserve Cells/ Squamous Metaplasia	Endocervical Columnar cells
	Basal	Parabasal	Intermediate	Superficial		
Growth factors/receptors						
Her 2/neu (Raju 1994)	+	+	–	–	+	+
EGF receptor (Raju 1994)	+	+	–	–	+	–
ER (Johnson 1973; Novotny et al. 1992; Pintos-Pascual et al. 2017)	+/–	+	+	–	+	+
PR (Johnson 1973; Novotny et al. 1992; Pintos-Pascual et al. 2017)	–	+*	–	–	+	+
Cell cycle proteins						
PCNA (Berchuck et al. 1990; Suh and Silverberg 1990; Bhagavan et al. 1982; Sharma 2015)	–	+	–	–	NA	+
MIB-1 (Ki-67) (Harnden et al. 1999; Hoosen et al. 1990)	–	+/–	–	–	–	–
Bcl-2 (Pintos-Pascual et al. 2017; Hoosen et al. 1990)	+		–	–	+	+/–
Cyclin B1 (Novotny et al. 1992)	–	+	–	–	?	?
Cyclin D1 (Cho et al. 1997)	+	+	–	–	+	+
Other proteins						
CD44 (Zhang et al. 2007)	+	+	–	–	+	–
Carcinoembryonic antigen (CEA)	–	–	–	–	–	+

*Expressed during luteal phase of menstrual cycle and during pregnancy

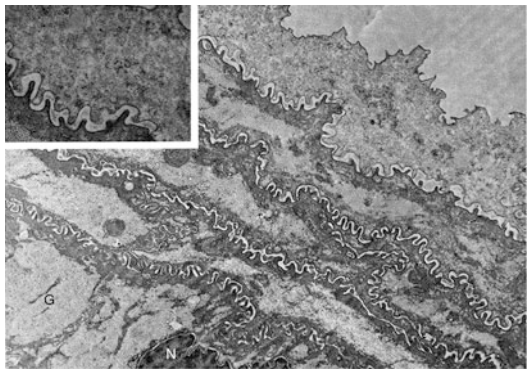

Fig. 5 Normal squamous epithelium. Electron microscopy of the superficial cells. These cells have pyknotic nuclei (N) and flattened cytoplasm packed with glycogen (G). The most superficial cells are rich in microfilaments and contain irregular surface membrane projections There is a lack of desmosomal attachments between the most superficial cells, a feature facilitating desquamation. *Inset*: Higher magnification of intracytoplasmic microfilaments in the most superficial cells.

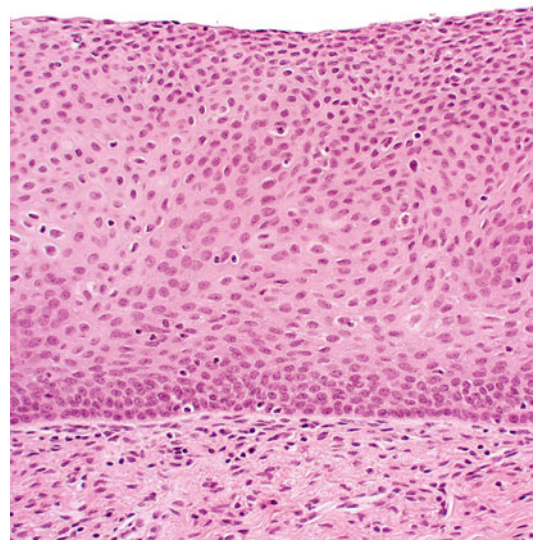

Fig. 6 Atrophic squamous epithelium. The epithelium is devoid of glycogen-rich vacuolated cells. The normal cellular orientation is disrupted, but cellular cohesion is normal and cytologic atypia is absent

whereas progesterone inhibits maturation at the upper midzone level of the epithelium. Accordingly, the portio epithelium during the postnatal period is fully mature and contains large amounts of glycogen as a result of maternal estrogen stimulation. Maturation ceases and glycogen rapidly disappears as the serum hormone levels fall. The epithelium remains atrophic during childhood until menarche when, under the stimulatory effect of ovarian hormones, maturation occurs again and glycogen reappears. During pregnancy, when progesterone levels are elevated, superficial cell maturation is absent.

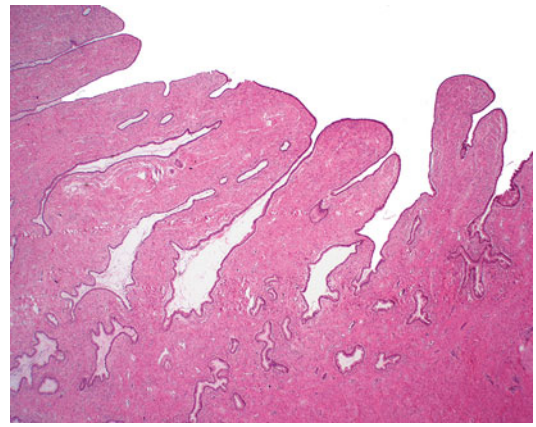

Fig. 7 Endocervical mucosa. There are cleft-like infoldings and tunnel-like collaterals. The neighboring gland-like structures represent tangentially sectioned cleft-tunnel complexes

Columnar Epithelium

Histology

A single layer of mucin-secreting, columnar epithelium lines both the surface of the endocervical canal and the underlying glandular structures. The latter are traditionally called *compound, tubular racemose, endocervical glands*. Three-dimensional plastic reconstructions from serial histological sections demonstrate that the endocervical glands actually represent deep, cleft-like infoldings of the surface epithelium with numerous blind, tunnel-like collaterals (Fig. 7) (Fluhmann 1961a). Because of the complex architecture of these clefts, or grooves, including oblique, transverse, and longitudinal arrangements, they appear as isolated glands in histological sections. The epithelium lining the clefts is identical with that lining the surface, and consequently the endocervical mucin-producing apparatus is not considered glandular but a complex infolding mucinous membrane. True glands, in contrast, have different epithelial lining in their secretory apparatus compared to their ductal and surface epithelial portions.

The columnar epithelial cells characteristically have basally placed nuclei and tall, uniform, finely granular cytoplasm filled with mucinous droplets (Fig. 8). The droplets have great affinity for Alcian blue stains, reflecting their sulfated, sialic acid, mucopolysacchride content (Fand 1973). Cells lining the luminal surface have been termed *picket cells* because of their resemblance to a picket fence. Occasionally, nonsecretory cells with cilia are observed (Fig. 9), the main function

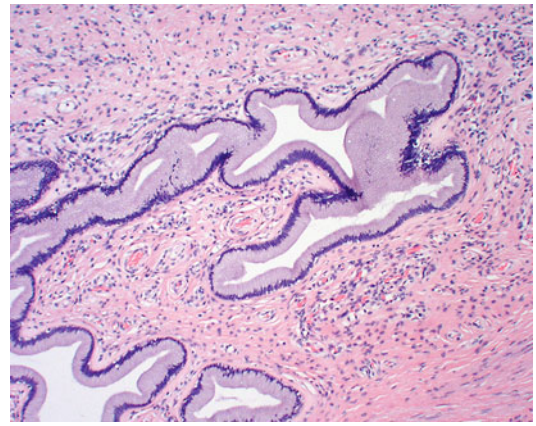

Fig. 8 Endocervical mucosa. Tall columnar mucin-filled endocervical cells with basal nuclei

of which is to distribute and mobilize the endocervical mucus (Gould et al. 1979). Isolated neuroendocrine, argyrophil, and argentaffin cell types also are identified within the endocervical epithelium by histochemical stains (Fetissof et al. 1991). The argentaffin-positive cells often contain serotonin. The physiologic purpose of these rare endocrine endocervical cells is obscure. Biochemically and immunohistochemically, the columnar cells of the endocervix have features of simple epithelia characterized by the presence of only low-molecular-weight cytokeratins, including cytokeratins 7, 8, 18, and 19 (Franke et al. 1986).

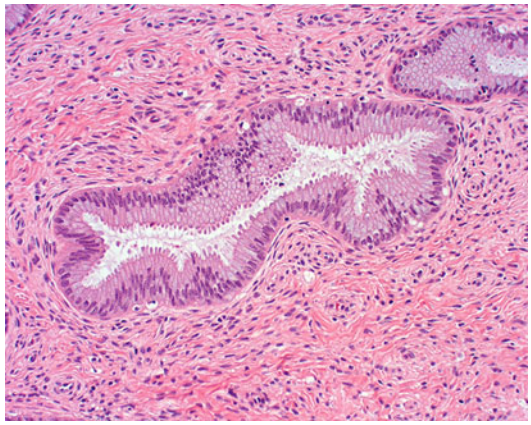

Fig. 9 Endocervical mucosa. Ciliated cells are frequently identified in the endocervical mucosa

Mitoses in the normal columnar epithelium are very rarely observed. It is not known whether regeneration occurs from the underlying subcolumnar reserve cells, which under normal circumstances are seldom seen even at the ultrastructural level, or from the persisting mature endocervical cells (Gould et al. 1979). Unlike the attenuated vascular stromal papillae of the original squamous portio epithelium, the subepithelial capillary network in the endocervical mucosa is well developed.

The stroma of the endocervix is comparatively better innervated than that of the exocervix. Fibers run parallel to muscle bundles, but sensory free endings have not been clearly demonstrated. True lymphoid follicles, with or without germinal centers, are encountered in the subepithelial stroma of both the exocervix and the endocervix.

Effects of Estrogen and Progesterone

The cervical mucus is subject to profound cyclic changes. Under estrogenic stimulation, the endocervical secretions are profuse, watery, and alkaline, facilitating sperm penetration. During the postovulatory phase, secretions are scant, thick, and acid, containing numerous leukocytes, and act as a barrier to sperm penetration. Endocervical secretory activity operates by both the apocrine and the merocrine type of expulsion of secretory products (Ferenczy and Richard 1974). In the former, a portion of apical cytoplasm packed with secretory granules is detached, whereas in the latter, secretory products are released from apical granules through pore-like openings of the surface cytoplasmic membrane.

Langerhans Cells and Lymphoid-Derived Cells

Mucosal immunity is an important component of the host's defense mechanism against viral and bacterial pathogens. Components of the secretory (IgA antibody-mediated), humoral (IgG antibody-mediated), as well as the cellular immune systems are present in the cervix. A variety of lymphocyte and dendritic macrophage subsets are present in both the epithelium of the exo- and endocervix as well as the subepithelial stroma (Manickam et al. 2007). Dendritic cells include both mature and immature forms. They are primarily responsible for antigen recognition and the earliest stage of cellular immune response.

Large numbers of T lymphocytes are also present in the cervix under normal conditions (Johansson et al. 1999). CD3+ T lymphocytes are concentrated in a band directly beneath both the squamous epithelium of the exocervix and the columnar epithelium of the endocervix (Johansson et al. 1999; Miller et al. 1992). These cells are predominately cytotoxic T-lymphocytes (e.g., CD8+), although helper T lymphocytes (e.g., CD4+) are also present. Variable numbers of B lymphocytes and plasma cells are also found in the lamina propria of the cervix (Johansson et al. 1999). Because the presence of lymphocytes as well as lymphoid follicles (Fig. 10) is a normal finding in the cervix, the diagnosis of chronic cervicitis should be reserved for specimens showing a marked infiltration of lymphocytes.

The Transformation Zone

The SCJ of the cervix is defined as the border between the stratified squamous epithelium and the mucin-secreting columnar epithelium of the endocervix. Morphogenetically, there are two different SCJ (Fig. 11). One is termed the *original* SCJ

and is the site at which the native squamous epithelium of the exocervix abuts the endocervical columnar epithelium at the time of birth. At birth, most newborns have some mucin-secreting columnar endocervical epithelium present on the exocervix which forms an *ectropion* or cervical *ectopy.* The exact location of the original SCJ and, therefore, the amount of endocervical ectopy present at birth depends on the extent of inward migration of squamous epithelium from the lower third of the vagina.

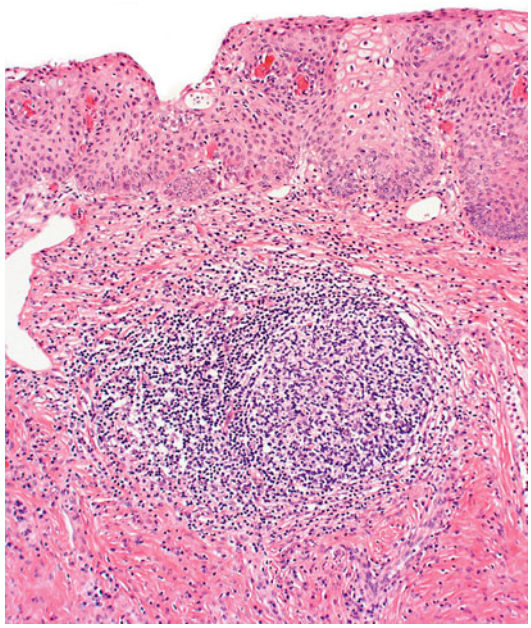

Fig. 10 Lymphoid follicles. Occasional lymphoid follicles can be seen in the cervical stroma in the absence of cervicitis

At about the age of 1 year, the cervix begins to elongate. This results in migration of the SCJ toward the external os. This migration is frequently incomplete. Hormonal and other physical factors influence the size and distribution of the cervical ectopy by altering the shape and volume of the cervical lips. At the time of menarche or during pregnancy, both the uterus and the cervix enlarge. Enlargement of the cervix is accompanied by alterations in its shape which result in more of an "eversion" or rolling outward of endocervical columnar epithelium onto the portio (Fig. 11). As a result, in most women during the reproductive period, cervical ectopy is present and the size of the ectopy is most extensive in women (under 20 years of age), and following the first pregnancy. When viewed with the naked eye, the endocervical mucosa appears as a red, velvety zone, sharply contrasting with the

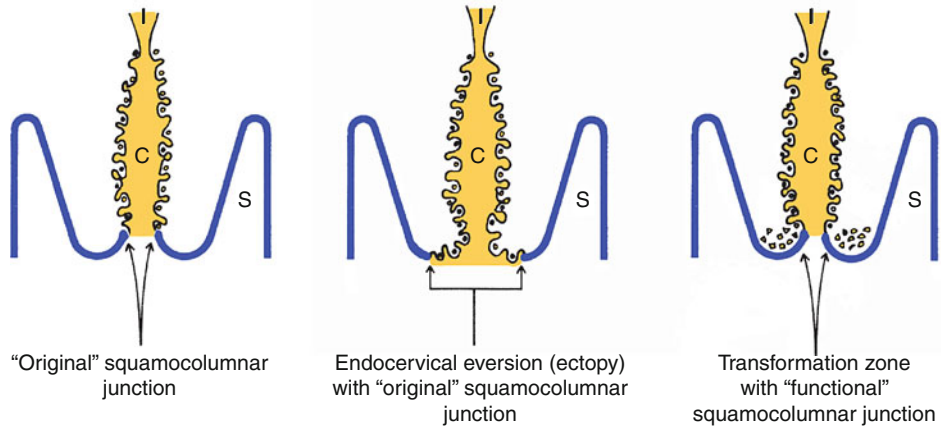

Fig. 11 The transformation zone. Schematic representation of original and functional SCJ and three basic types of portios. *Left:* Diagram of a portio completely covered with native squamous epithelium. The SCJ is at the external os. *Middle*: Denotes cervical ectopy, with the SCJ being located on the exocervix below the external os. *Right*: Indicates areas of cervical ectopy that have become covered with squamous epithelium. This area is the cervical transformation zone. The new, or functional, SCJ of the transformation zone is at the external os. S, squamous epithelium: C, endocervical columnar epithelium; I, uterine isthmus

neighboring pink, translucent squamous portio epithelium (Fig. 12a).

Over time, the columnar epithelium that composes the cervical ectopy is remodeled and replaced by metaplastic squamous epithelium. As this occurs, the histological squamocolumnar junction moves toward the exocervical os. This newly formed SCJ is called the *physiologic*, *functional*, or *new* SCJ. While the original SCJ is usually quite abrupt, the junction between the columnar and squamous epithelium at the physiologic or functional SCJ can be either abrupt or gradual (Fig. 12). The region between the original SCJ and the post-pubertal functional SCJ is termed the *transformation zone.* The transformation zone is histologically characterized by the presence of metaplastic epithelium (see section "Squamous Metaplasia").

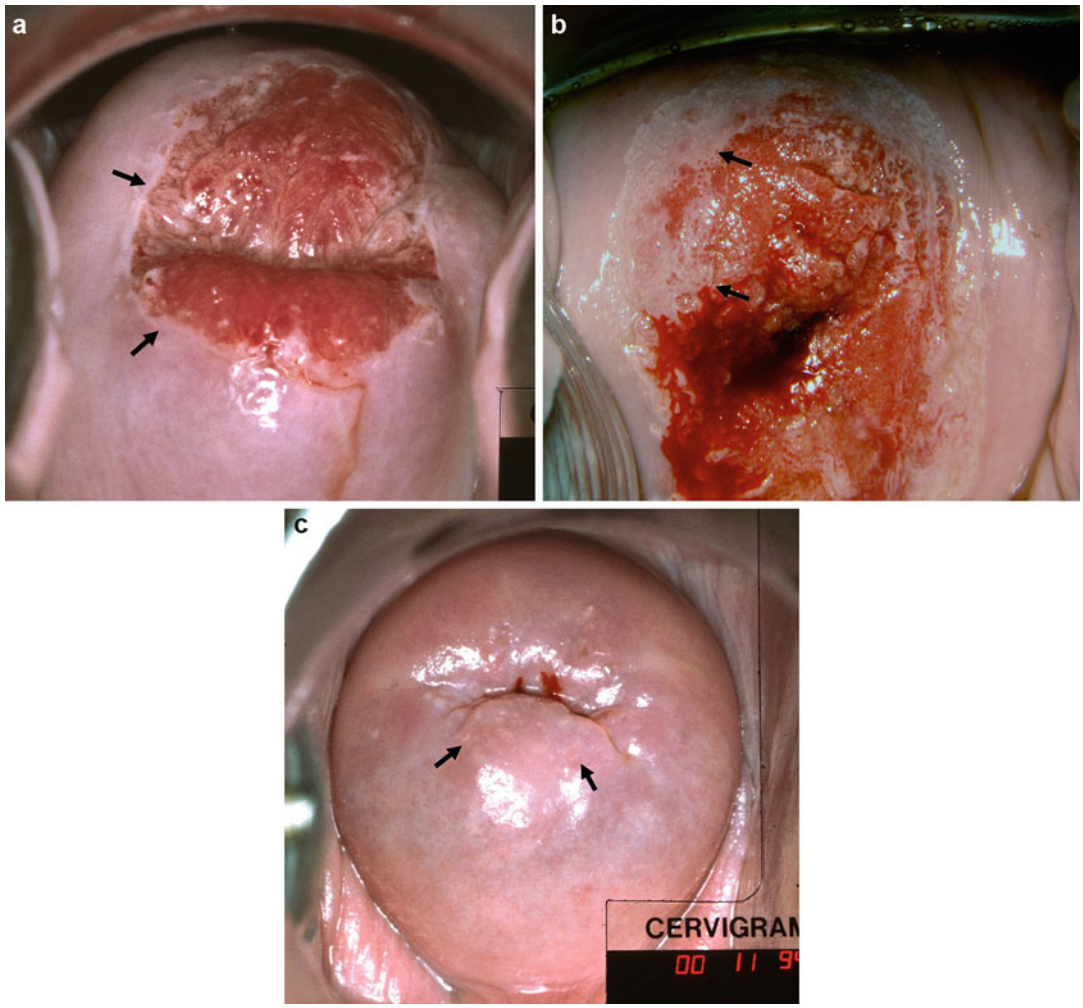

Fig. 12 The transformation zone. Colpophotographs of endocervical eversion of the transformation zone. *Top:* Endocervical mucosa is everted on both the anterior and the posterior lip and surrounds the anatomic external os. The original SCJ is on the portio of the cervix (arrows). *Middle:* Squamous metaplasia is occurring and the new SCJ (arrows) is now internal to the original SCJ. The area between the original and new SCJ is the transformation zone. *Bottom:* The transformation zone is completely mature and the SCJ is inside the endocervical canal. Residual endocervical gland mouths are represented by the circular openings (arrows)

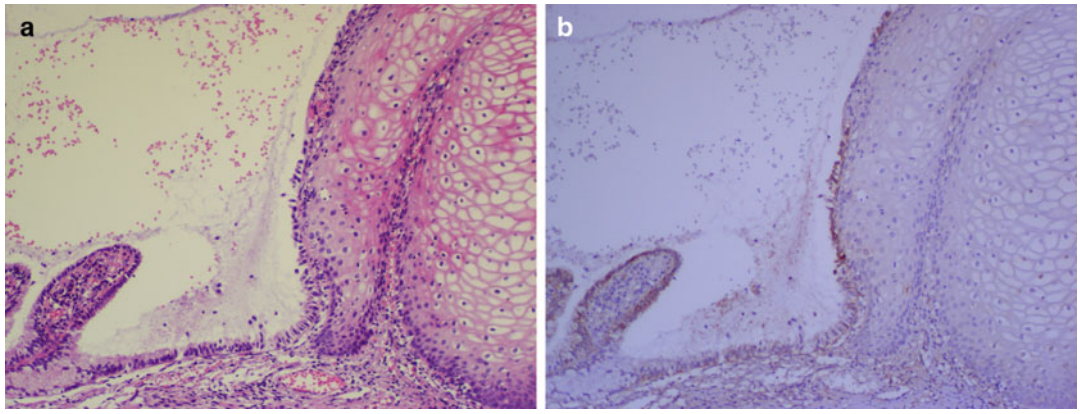

Fig. 13 SC junctional cells. (**a**) A discrete population of cuboidal epithelial cells are found at the SCJ. (**b**) The cells have a unique immunophenotype and stain positively for cytokeratin 7 whereas the adjacent squamous epithelium and columnar endocervical cells do not. (Figure provided by Drs. Christopher Crum and Michael Herfs)

The concept of the transformation zone is extremely important for understanding the pathogenesis of squamous cell carcinomas of the cervix and its precursors, since virtually all cervical squamous neoplasia begins at the new SCJ and because the extension and limits of cervical cancer precursors coincide with the distribution of the transformation zone. It is also important to remember that during the childbearing years and during pregnancy the transformation zone is located, in almost all instances, on the exposed portion of the cervix. Consequently, the vast majority of cervical neoplasias can be sampled for histologic diagnosis by punch biopsy. Movement of the functional SCJ continues throughout the reproductive years. Therefore, in older and postmenopausal women, the functional SCJ is nearly always located within the external os (Fig. 12).

The association between the transformation zone and the development of cervical neoplasia may be explained by the relatively recent discovery of a discrete population of cuboidal epithelial cells that reside at the SCJ (Herfs et al. 2012). These epithelial cells form a single layer and their location is consistent regardless of whether the SCJ separates the native portio squamous epithelium or metaplastic squamous cells from the endocervical columnar cells (Fig. 13a). Because of their unique histological features, these cells are called "SC junctional cells" (Herfs et al. 2012). The SC junctional cells have a unique immunophenotype compared to either squamous cells or endocervical columnar cells. They stain positively for cytokeratin 7, anterior gradient (AGR)2, cluster differentiation (CD) 63, matrix metalloproteinase (MMP)7, and guanine deaminase (GDA), whereas squamous cells and endocervical columnar cells do not (Fig. 13b).

Cervical high-grade squamous intraepithelial lesions (HSIL) that are high-risk human papillomavirus (HPV) positive and invasive cervical cancers have been shown to have the SC junctional cell immunophenotype, whereas ectocervical low-grade squamous intraepithelial lesions (LSIL) and vulvar and vaginal squamous epithelial lesions (SILs) of both grades do not (Herfs et al. 2012). Therefore, it is thought that the SC junctional cells are the target cells for high-risk HPV infections that can progress to cervical HSIL or invasive cervical cancer.

Pregnancy and Puerperium

The morphologic alterations that occur in the antepartum or postpartum cervix are not pathognomonic of pregnancy or parturition but are seen more commonly at these times than in the nonpregnant postpartum state. They are related to the stimulatory

effects of elevated steroid hormones. The spongy enlargement of the pregnant cervix is caused by increased vascularity and edema of the stroma accompanied by acute inflammation. The massive destruction of collagen fibers and accumulation of extracellular glycoprotein ground substance before labor result in cervical softening and effacement, facilitating dilation of the cervix to about 10 cm during labor. Gestational cervical mucus is thick, tenacious, rich in leukocytes, and forms a mucous plug that obliterates the cervical canal, sealing the endometrial cavity from the vagina and thus preventing bacterial invasion. Squamous metaplasia and lobules of tightly-packed, small endocervical glandular units forming polypoid protrusions into the canal are often seen.

Pseudodecidual Reaction

Pseudodecidualization of the stroma, either patchy or diffuse, occurs in about one-third of the cervices examined histologically and disappears by 2 months postpartum (Johnson 1973). It is presumably mediated by the high levels of progesterone during pregnancy. The appearance of pseudodecidualized cervical stroma is identical to decidualized stroma at other sites. The cells develop abundant pink cytoplasm, with well-defined cellular borders (Fig. 14a, b).

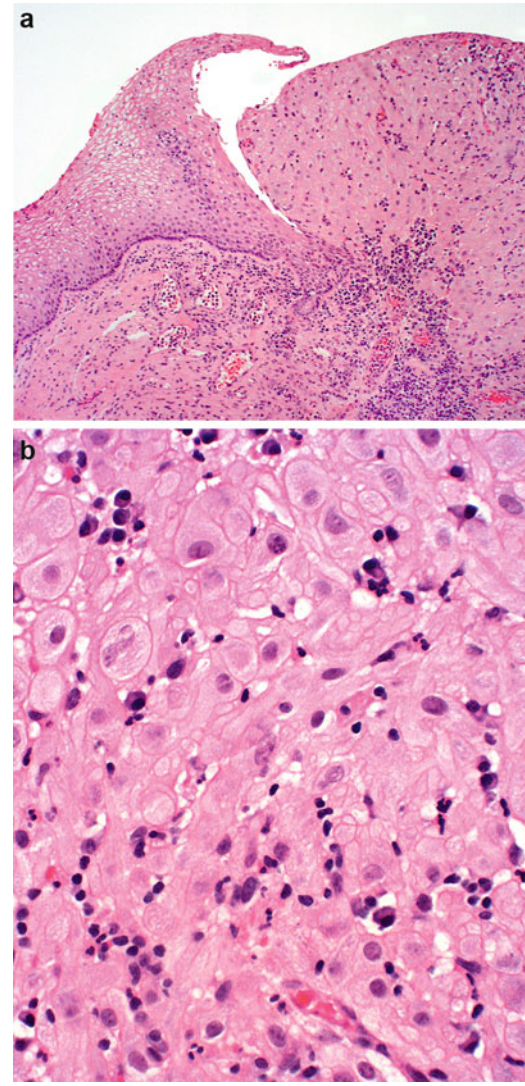

Fig. 14 Pseudodecidual reaction. A pseudodecidual reaction of cervical stromal cells can occur during pregnancy. (**a**) In this case, the pseudodecidual reaction forms a discrete nodule. (**b**) The decidualized stromal cells are identical with gestational decidual cells of the endometrium

Arias-Stella Reaction

During pregnancy, the gestational Arias-Stella reaction can develop in both endocervical glands and ectopic endometrial glands within the cervix. In one study of 191 gravid hysterectomy specimens, an Arias-Stella reaction of endocervical glands was seen, at least focally, in 9% of the cases (Schneider 1981). The Arias-Stella reaction of the endocervix is usually focal and is more commonly present in the proximal portion of the endocervix involving superficial as opposed to deeply situated glands. Microscopically, the Arias-Stella reaction that occurs in the endocervical glands during pregnancy is identical to that which occurs in the endometrium. The cells within the affected glands are markedly enlarged with irregular, frequently hyperchromatic nuclei that can project into the glandular lumen in a hobnail pattern. The cells are pseudostratified and have hypersecretory cytoplasmic features with abundant vacuolated cytoplasm (Fig. 15). Papillary processes with fibrovascular cores lined by enlarged epithelial cells can project into the endocervical gland lumen.

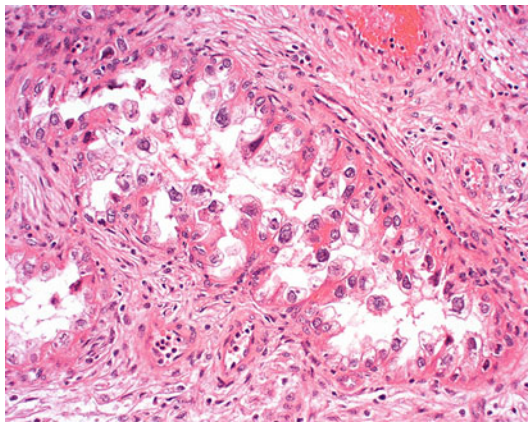

Fig. 15 Arias-Stella reaction. The Arias-Stella reaction should not be confused with clear cell adenocarcinoma of the cervix

The Arias-Stella reaction can occasionally be mistaken for clear cell carcinoma or adenocarcinoma in situ (AIS) of the cervix. Differentiation from clear cell carcinoma is made by the lack of a mass lesion and clear cut stromal invasion as well as by the absence of the classic tubular and papillary areas typical of clear cell carcinoma. The cells in AIS have more uniform nuclei and less cytoplasmic vacuolization. The Arias-Stella reaction lacks mitotic activity whereas both clear cell carcinoma and adenocarcinoma in situ are mitotically active. Because of the possibility of confusing Arias-Stella reaction with clear cell carcinoma or AIS, the diagnosis of the later two entities should be made with caution in the pregnant patient.

Metaplasia

Squamous Metaplasia

Metaplasia is defined as the replacement of one type of mature tissue by another equally mature type of tissue. In the cervix, squamous metaplasia is the replacement of the mucin-producing columnar epithelium by stratified squamous epithelium and appears to occur by two different mechanisms (Fig. 16). One mechanism consists of direct ingrowth from the native portio epithelium bordering the columnar epithelium, a process frequently referred to as "squamous epithelialization." The second mechanism involves a proliferation of undifferentiated subcolumnar reserve cells of the endocervical epithelium, which differentiate into squamous epithelium. This process has been termed *squamous metaplasia*.

During squamous epithelialization, tongues of native squamous epithelium of the portio grow beneath the adjacent columnar epithelium and expand between the mucinous epithelium and its basement membrane. As the squamous cells expand and mature, the endocervical cells are gradually displaced upward, degenerate, and eventually are sloughed (Fig. 17). The progression of squamous transformation of the endocervical ectropion has been hypothesized to be primarily dependent on local (vaginal) environmental factors initiated by the low (acid) pH of the vagina after puberty (Coppleson et al. 1971). Trauma, chronic irritation, or cervical infection also play a role in development and maturation of the transformation zone by stimulating repair and remodeling; eventually, the ectocervix is covered by a protective surface of mature squamous epithelium (Fig. 18). The process of squamous epithelialization is thought to be responsible for the obliteration of the outer two-thirds of endocervical ectopy. Rapid squamous re-epithelialization of the columnar epithelium of the transformation zone may also be produced iatrogenically by electrocautery, cryosurgery, or laser surgery.

The second mechanism involved in replacement of columnar epithelium by a squamous epithelium and the formation of the transformation zone is squamous metaplasia. The first stage of squamous metaplasia is the appearance of small cuboidal cells beneath the columnar mucinous epithelium, the so-called subcolumnar reserve cells (Fig. 19). *Reserve cells* have large, uniformly-shaped, round nuclei with faintly granular chromatin and occasional aggregates of chromatin (i.e., chromocenters of reserve cells). The cell borders are poorly defined and the cells have only scant amounts of cytoplasm. The origin of subcolumnar reserve cells is controversial. Some investigators suggest a direct derivation from

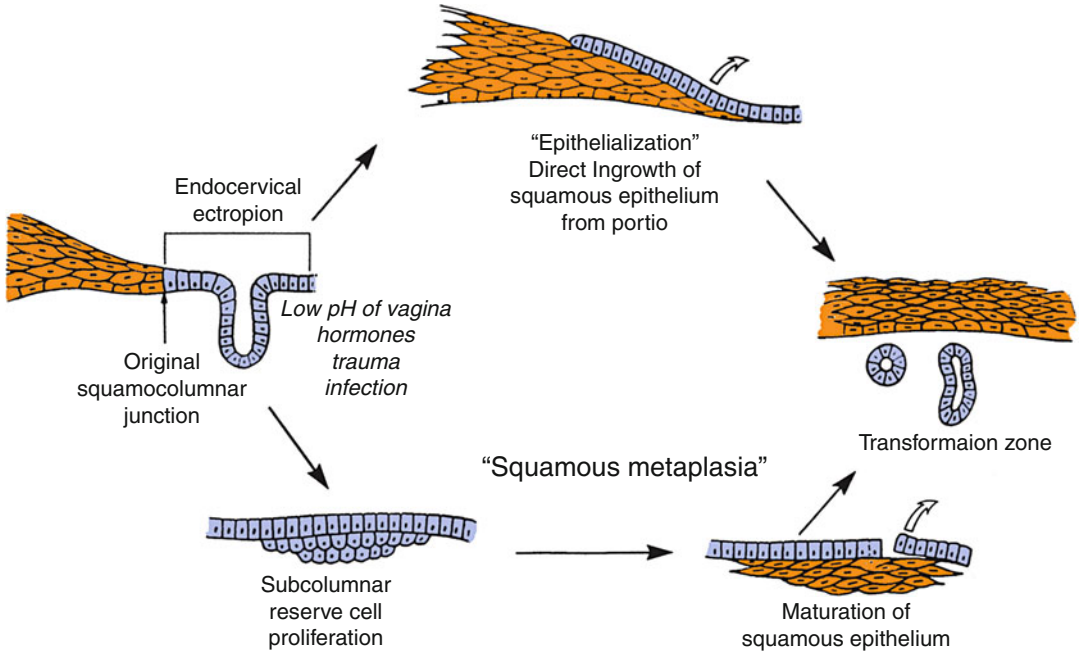

Fig. 16 Squamous metaplasia. There are two histogenic mechanisms by which the endocervical mucosa is replaced by squamous epithelium. The first is the direct ingrowth of squamous epithelium from the portio, which is referred to as squamous epithelialization (top). The other is through proliferation of subcolumnar reserve cells and their subsequent maturation into a squamous epithelium, which is called squamous metaplasia (bottom). Both result in a mature squamous epithelium overlying endocervical mucus-producing glands (right)

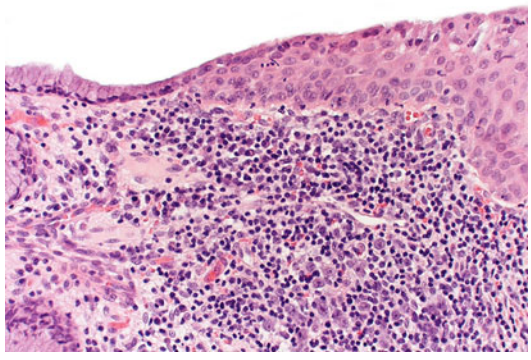

Fig. 17 Squamous epithelialization. During squamous epithelialization, a narrow tongue of squamous epithelium from the portio grows under the everted endocervical mucosa and lifts it off the basement membrane. The endocervical cells then degenerate and are sloughed

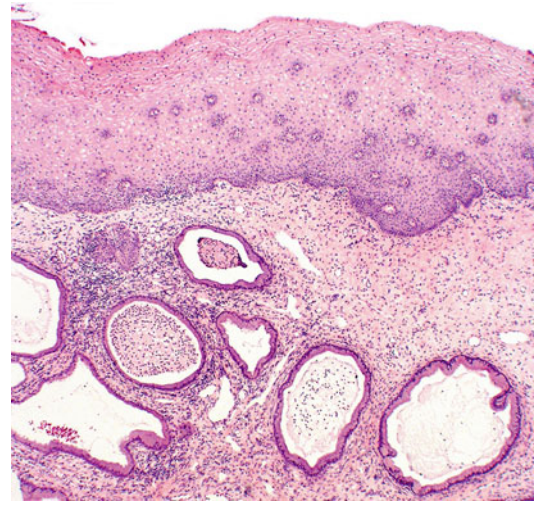

Fig. 18 Mature transformation zone. Mature squamous epithelium covers the underlying endocervical glands that are distended with mucin

columnar mucinous secretory cells, whereas others favor an origin from the basal cells of the squamous portio epithelium, embryonal rests of urogenital origin, or stromal cells as possible sources.

Progressive growth and stratification of reserve cells (subcolumnar reserve cell hyperplasia), followed by differentiation into immature squamous

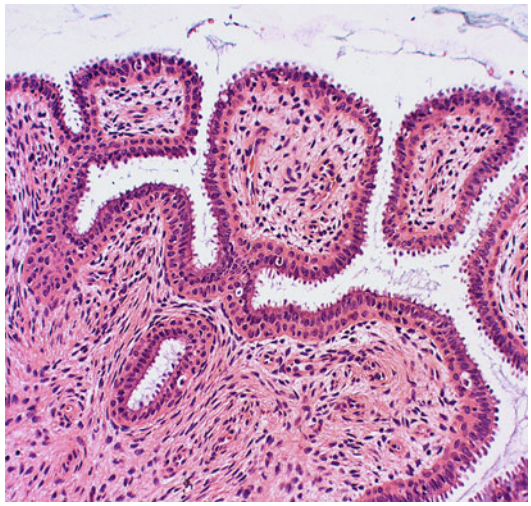

Fig. 19 Reserve cell hyperplasia. Reserve cells are seen under the columnar epithelium

metaplasia followed by additional maturation, result in the formation of a fully mature squamous epithelium indistinguishable from the native portio epithelium (Figs. 20a–c and 21). Immature squamous metaplastic epithelium is distinguished from its mature counterpart by a lack of surface maturation and inconspicuous intracytoplasmic glycogen. It is, characteristically, sharply demarcated from the native portio epithelium by a perpendicular or oblique line to the surface. As a result, the uninitiated observer may mistake immature squamous metaplasia for a HSIL, particularly when the process also involves the underlying glands. In contrast to neoplastic epithelium, the immature squamous metaplastic epithelium maintains cell organization and cohesion, nuclear atypia is absent, and, frequently, a single row of endocervical cells overlies the squamous cells. Biochemically and immunohistochemically, immature squamous metaplasia shares features of both the mature squamous epithelium and the columnar mucinous epithelium. p16 immunohistochemical staining has been shown to be a very useful way of differentiating immature squamous metaplasia from HSIL (Bergeron et al. 2010; Zhang et al. 2007; Klaes et al. 2001; Wang et al. 2004; Jonasson et al. 1992). Immature squamous metaplasia does not stain with p16 (Fig. 22a, b) whereas almost all HSIL will show strong diffuse basal and parabasal staining.

Tubal Metaplasia

Tubal metaplasia refers to endocervical glands that are lined by a Mullerian-type epithelium that closely resembles that of the fallopian tube. In pure tubal metaplasia, the endocervical glands are lined by an epithelium that more closely resembles that of the fallopian tube and contains many more ciliated cells than are normally present in the endocervical epithelium as well as tubal type secretory cells and reserve or intercalated cells (Fig. 23a, b) (Jonasson et al. 1992; Novotny et al. 1992; Suh and Silverberg 1990). Tubal metaplasia can be found in up to 31% of patients and does not appear to be related to the phase of menstrual cycle, the presence of inflammatory changes, or LSIL (CIN 1) (Jonasson et al. 1992).

Tubal metaplasia can be quite extensive and can occasionally be mistaken for endocervical glandular neoplasia. However, the bland cytological features, lack of mitotic activity, and prominent cilia seen at the apical surfaces of tubal metaplasia usually allow it to be differentiated from a neoplastic lesion. Other features that can aid in distinguishing between tubal metaplasia and glandular neoplasia are the location and shape of the glands and the surrounding stroma. Glands demonstrating tubal metaplasia are typically confined to the superficial third of the cervical wall (i.e., they extend less than 7 mm into the cervical stroma) and typically show only slight variation in size and shape. Moreover, the stroma surrounding glands involved by tubal metaplasia is usually normal appearing and is neither desmoplastic nor edematous appearing. Cases of tubal metaplasia demonstrating glandular architectural abnormalities or hypercellularity of the adjacent stroma can present diagnostic difficulties (Oliva et al. 1995).

Atypical tubal metaplasia is a form of tubal metaplasia in which the glands are lined by ciliated and nonciliated cells that are crowded and have larger, more hyperchromatic nuclei than observed in typical tubal metaplasia (Fig. 24). The cells of atypical tubal metaplasia are frequently pseudostratified. Atypical tubal metaplasia frequently presents a diagnostic problem since it histologically can be confused with

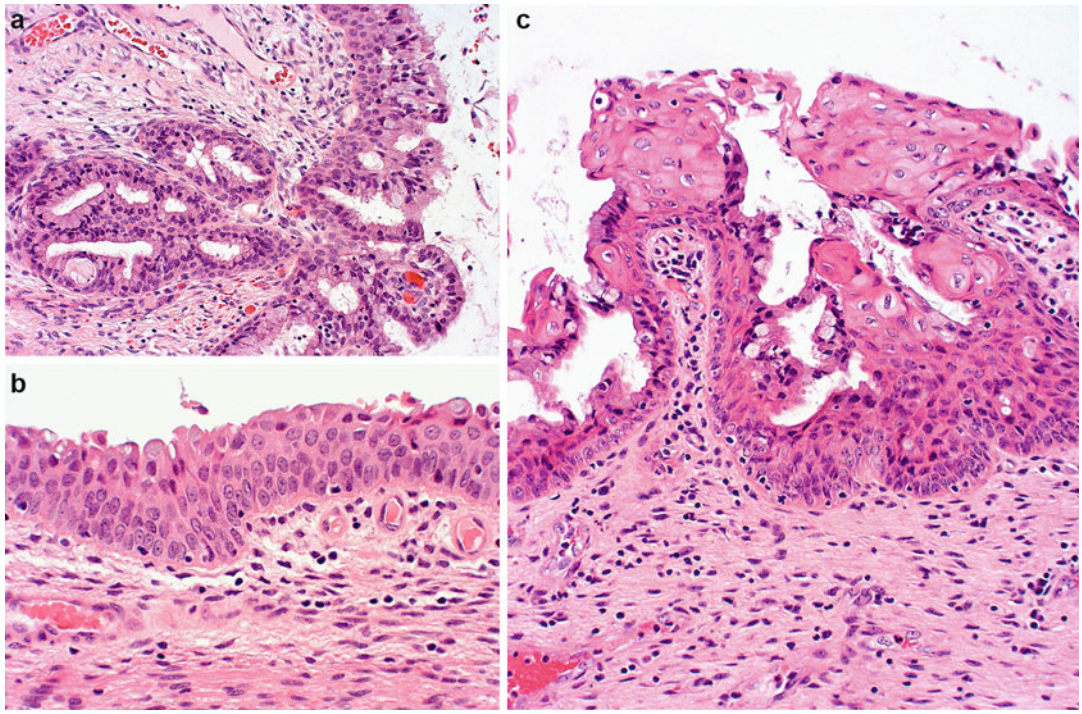

Fig. 20 Squamous metaplasia. (**a**) Reserve cells proliferate and begin to stratify under the columnar epithelium. (**b**) Columnar differentiation begins to be lost, resulting in a multilayered squamous epithelium composed of immature metaplastic cells. Note occasional mucinous endocervical cells at the surface. (**c**) The immature metaplastic epithelium begins to differentiate

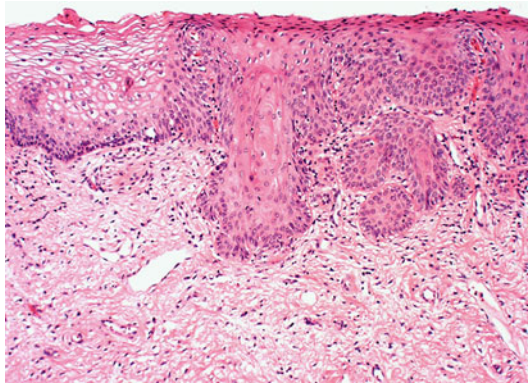

Fig. 21 Transformation zone epithelium. On the left, the native portio epithelium is present with full maturation. On the right, metaplastic squamous epithelium is present. Note the sharp boundary. Metaplasia has extended into the endocervical crypts and completely replaced the columnar epithelium

AIS. Differentiation from AIS is based on a lack of significant mitotic activity, the absence of architectural abnormalities such as cribiforming and papillary projections, and usually a lack of diffuse p16 positivity. An occasional isolated gland can have diffuse p16 positivity but the entire metaplastic lesion should not be diffusely p16 positive. However, it should be cautioned that atypical tubal metaplasia can occur in association with AIS of the cervix, including both tubal and non-tubal types (see ▶ Chap. 5, "Precancerous Lesions of the Cervix").

Tubo-Endometrioid Metaplasia

Tubo-endometrioid metaplasia of the cervix is a type of metaplasia that is histologically similar to the tubal metaplasia that can develop in the endometrium in patients with unopposed estrogenic stimulation. Endocervical glands demonstrating tubo-endometrioid metaplasia are lined by a pseudostratified epithelium composed of columnar cells with a high nuclear:cytoplasmic ratio

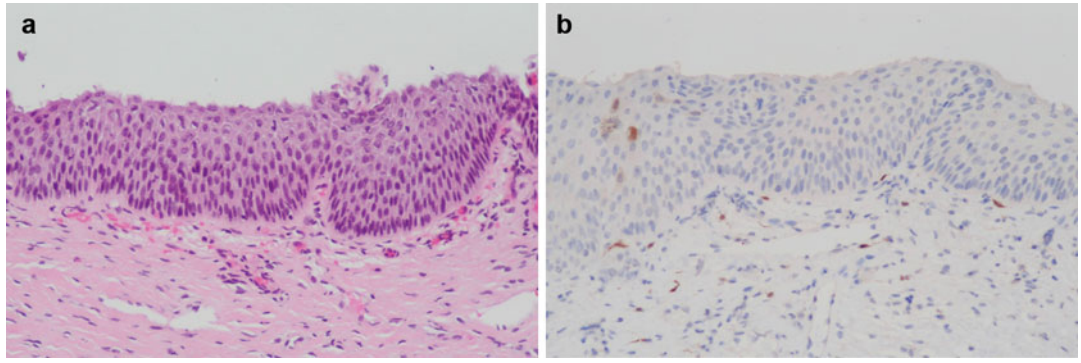

Fig. 22 Immature squamous metaplasia. (**a**) Using hemotoxylin and eosin (H&E) staining alone, it can be difficult to distinguish between immature squamous metaplasia and HSIL. (**b**) However, using immunohistochemistry for p16, the distinction is obvious since metaplasia does not stain for p16 whereas HSIL will

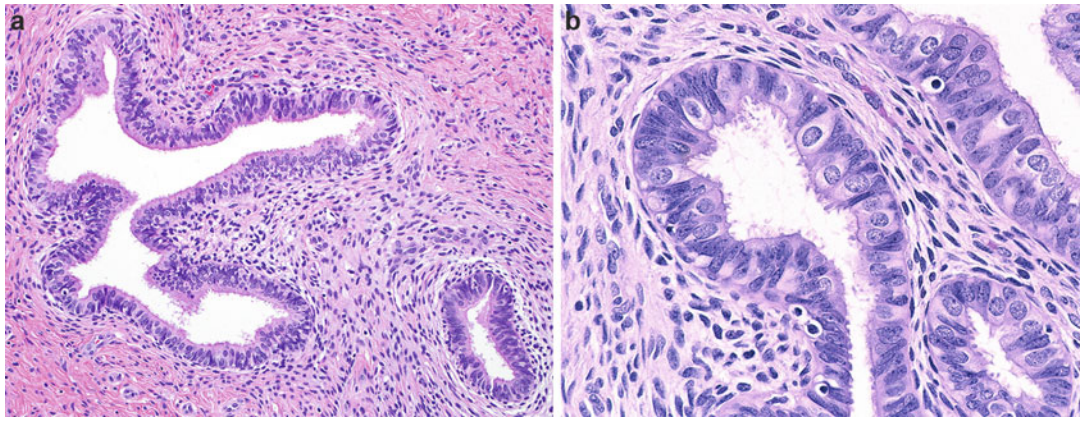

Fig. 23 Tubal metaplasia. (**a**) The columnar, mucus-producing epithelium has been replaced by a tubal type epithelium with ciliated, secretory and intercalated cells (**b**) At higher magnification, the resemblance to the epithelium of the fallopian tube is obvious

(Fig. 25). Many of these cells are ciliated or have secretory features with apical snouts but the glands lack an associated endometrial stroma. Tubo-endometrioid metaplasia occurs commonly after cervical conization and has been interpreted as a form of aberrant differentiation following cervical injury (Ismail 1991). Because of the pseudostratification and high nuclear:cytoplasmic ratio, these glands can be misinterpreted as representing AIS. As with tubal metaplasia, the features that indicate a metaplastic, as opposed to a neoplastic, process are the lack of atypia and lack of diffuse p16 positivity. The retention of an architecture conforming to the normal pattern of endocervical glands and lack of a desmoplastic or edematous stromal response are features that can assist in differentiating this form of metaplasia from invasive adenocarcinoma.

Transitional Cell Metaplasia

Transitional cell metaplasia refers to a controversial type of metaplasia in which the surface of the cervix and endocervical crypts is lined by an epithelium that is interpreted by some to resemble a hyperplastic urothelium (Duggan 2000; Egan and Russell 1997; Jones 1998; Weir et al. 1997). By definition, the epithelium has a "disordered" appearance that is comprised of over 10 layers of

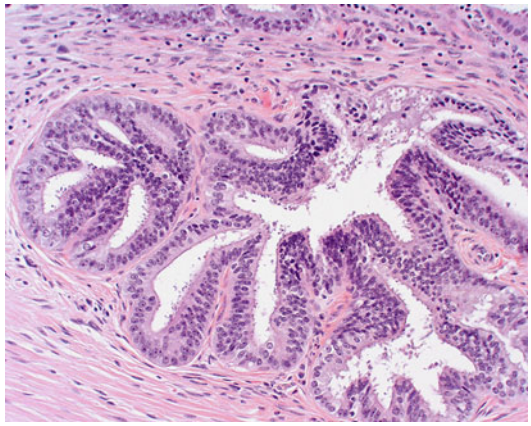

Fig. 24 Atypical tubal metaplasia. The epithelium is more crowded and pseudostratified than seen in typical tubal metaplasia. The cells have larger, hyperchromatic nuclei. Ciliated cells are present, but mitotic figures are uncommonly seen

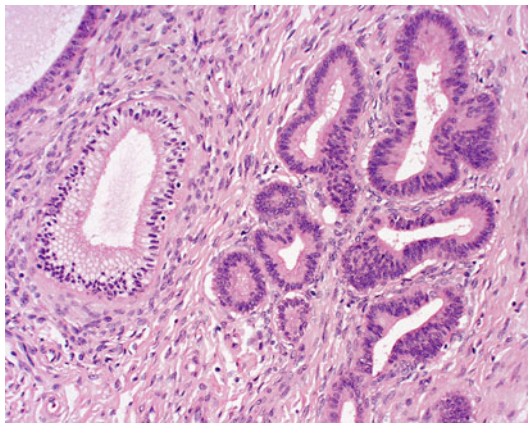

Fig. 25 Tubo-endometrioid metaplasia. Typical endocervical epithelium is seen on the left. On the right columnar, mucus-producing epithelium has been replaced by a pseudostratified epithelium with a high nuclear: cytoplasmic ratio and with cilia and apical snouting

cells that have oval to spindle-shaped nuclei and are oriented vertically in the deeper layers (Fig. 26). The cells of the superficial layer often resemble the umbrella cells of the normal urothelium and have horizontally oriented nuclei.

The controversy surrounding transitional cell metaplasia revolves around whether it represents a unique histopathological entity that has a specific biology or whether it simply represents a biologically insignificant histological variation of other well described histological entities. Almost all of

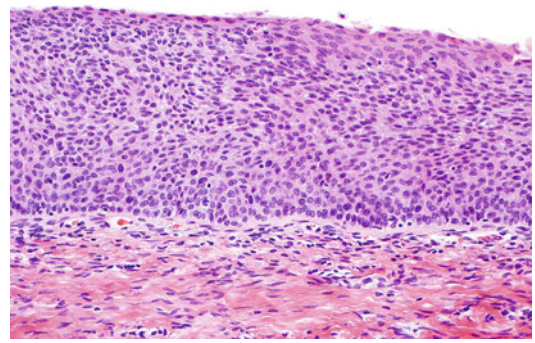

Fig. 26 Transitional cell metaplasia. The squamous epithelium in this postmenopausal patient is more than 10 layers thick and is disorganized. This type of change is referred to by some as "transitional cell metaplasia"

the reported examples of transitional cell metaplasia have been identified in postmenopausal women. In the two largest series, the mean ages of women with the lesion were 60 and 67.8 years (Egan and Russell 1997; Weir et al. 1997). Some of these women have had previous abnormal Papanicolaou smears, and it has been suggested that some of the cases may represent atrophic HSIL (Koss 1998). In addition to arising in the transformation zone, transitional cell metaplasia can also be identified in the exocervix and the vagina (Weir et al. 1997). This suggests that in some cases, transitional cell metaplasia may simply represent a histological variant of atrophy, either of the original squamous epithelium or of a fully mature metaplastic squamous epithelium, in which the number of cell layers is not reduced. Immunohistochemical studies using cytokeratin antibodies have shown that foci of transitional cell metaplasia express cytokeratins 13, 17, and 18, which are expressed in normal urothelium, but do not express cytokeratin 20 and the asymmetric unit membrane that are related to urothelial differentiation (Harnden et al. 1999). Lack of diffuse p16 positivity helps to differentiate transitional cell metaplasia from HSIL.

Inflammatory Diseases

Cervicitis can be divided into two categories, based on whether the etiology of the disorder is noninfectious or infectious. Whatever the etiology, the tissue response of the cervix to injury is limited

and reflects the basic mechanisms of inflammation and repair. Two types of morphologic changes, however, that are often encountered in association with a variety of inflammatory diseases deserve specific attention. These are atypia of repair and hyperkeratosis and parakeratosis.

Atypia of Repair

In cases of severe, acute long-standing chronic inflammation or infection with epithelial injury of any kind – true erosion, biopsy, or conization – the squamous and endocervical epithelia undergo reactive changes characterized by epithelial disorganization and nuclear atypia. These changes are often confused, histologically and cytologically, with HSIL. In reactive squamous atypia, the cytoplasmic membrane is well defined, the nuclei are uniform in shape and size, and the chromatin is aggregated in prominent aggregates or clumps (Fig. 27a, b). The epithelium is often infiltrated with migrating inflammatory cells. Mitotic figures are normal and are confined to the proliferative basal and parabasal cell populations. Characteristically, the cells in the upper half of the epithelium are normal, and maturation occurs in an orderly fashion.

When reparative changes affect endocervical columnar cells, the morphological alterations include nuclear enlargement and hyperchromasia with irregularity of nuclear size and shape and smudgy chromatin. There can also be cytoplasmic eosinophilia, and loss of mucinous droplets (Fig. 28a, b). The combination of endocervical cell enlargement with dense, eosinophilic, focally vacuolated cytoplasm and varying degrees of nuclear atypia has been referred to as "atypical oxyphilic metaplasia". Although this type of glandular epithelium appears atypical, the changes are focal, alternating with normal mucinous columnar cells, and are confined to areas with inflammation or mucosal injury. In addition, the deep

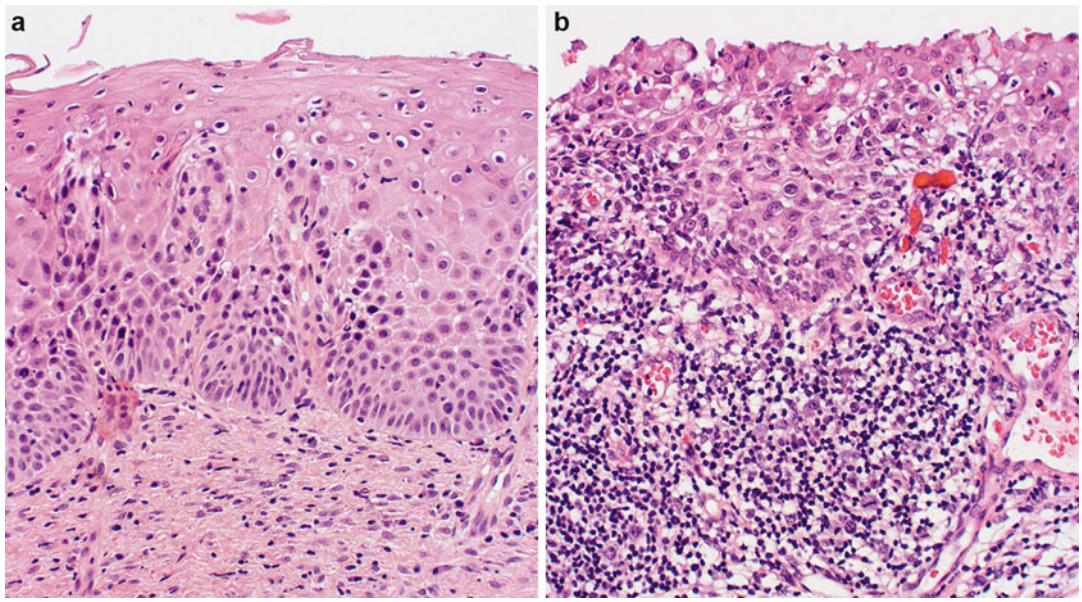

Fig. 27 Squamous reparative atypia. (**a**) When reparative changes develop in mature squamous epithelium, there is usually basal cell hyperplasia that involves the lower one third of the epithelium. The nuclei contain prominent chromocenters but lack nuclear abnormalities associated with neoplasia. Intermediate and superficial epithelial cells continue to show maturation, but often develop perinuclear halos and some degree of nuclear enlargement. However, the superficial cells lack the nuclear atypia characteristic of HPV-infected cells. (**b**) When reparative changes develop in immature metaplastic squamous epithelium, the epithelium exhibits intercellular edema and acute and chronic inflammatory cells often infiltrate both the epithelium and stroma. The nuclei of the metaplastic cells become hyperchromatic and enlarged and typically have prominent chromocenters. Microabsesses are frequently seen

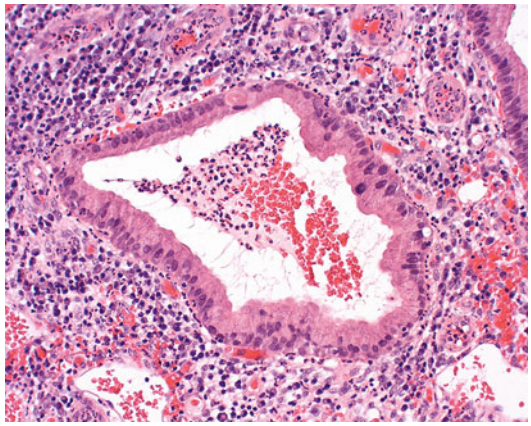

Fig. 28 Endocervical reparative atypia. The endocervical epithelium develops nuclear enlargement, mitosis, microabscesses, and inconspicuous intracellular mucus. Note the diffuse distribution of nuclear chromatin, the cytoplasmic eosinophilia, and the absence of abnormal mitoses, features distinguishing endocervical atypia of inflammation from AIS of the cervix

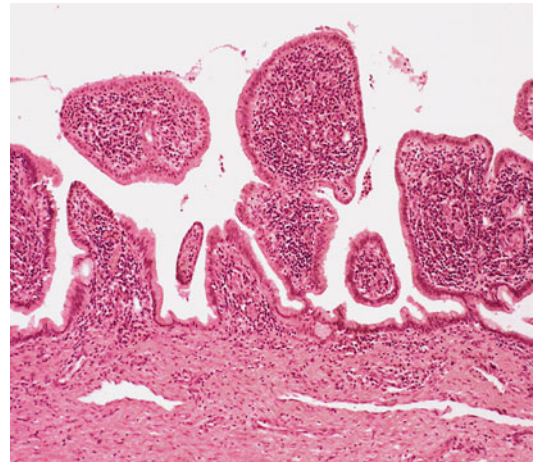

Fig. 29 Papillary endocervical reparative change. The marked inflammation of the stroma results in endocervical epithelium being raised into papillary projections

cytoplasmic eosinophilia, when it is present, and the absence of abnormal mitoses are features that distinguish the inflammatory lesions from an AIS of the endocervix. In both squamous and endocervical cell atypia of repair, immunostaining for $p16^{ink}$ is uniformly negative. This marker is of great help for distinguishing HSIL and AIS from their mimic, e.g., epithelial atypia of repair. Occasionally when there is endocervical inflammation, the stroma becomes filled with chronic inflammatory cells and this results in the endocervix taking on a papillary configuration (Fig. 29).

Radiation-Induced Atypia

Treatment of the cervix with therapeutic levels of radiation can cause morphological changes in both the squamous and glandular epithelium. The atypical squamous cells that develop post radiation have nuclear enlargement and can be multinucleated. The cells can have abundant amounts of vacuolated cytoplasm and are usually detected in cervical cytological preparations. Radiation-induced changes in the endocervical glandular epithelium include cellular enlargement, a loss of polarity of nuclei, and dense eosinophilic, enlarged nucleoli that can be multiple (Mohan et al. 1999). The stroma in women who have received therapeutic radiation is frequently fibrotic, often with hyalinization. Blood vessels often have intimal hyaline thickening and can be totally occluded. Atypical fibroblasts that are sometimes referred to as "radiation fibroblasts" are usually not present (Lesack et al. 1996). These morphological changes can exist for many years after radiation therapy.

Hyperkeratosis and Parakeratosis

Hyperkeratosis and parakeratosis can be detected cytologically in up to 8% of all women undergoing routine Pap smear screening (Johnson et al. 1991). Both hyperkeratosis and parakeratosis have the gross appearance of a thickened, white epithelium and can be either focal or diffuse. When diffuse, the entire portio is covered by a thickened, white, and wrinkled epithelial membrane. When focal, a slightly raised white plaque is present. The etiology of cervical hyperkeratosis is poorly understood, but in some cases, it appears to be related to chronic irritation. For example, most patients with diffuse hyperkeratosis have

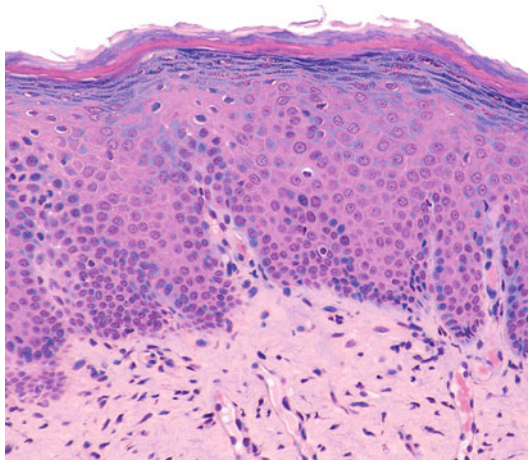

Fig. 30 Hyperkeratosis of the cervix. A superficial layer of anucleated, keratinized squamous cells which is frequently accompanied by a thickened granular layer is present

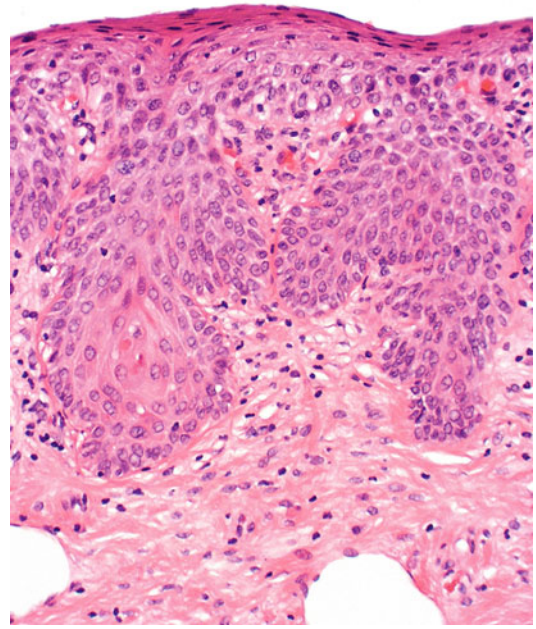

Fig. 31 Parakeratosis of the cervix. Pyknotic nuclei are retained in the superficial cell layer. Parakeratosis is frequently accompanied by hyperkeratosis

prolapsed uteri. Focal areas of hyperkeratosis can be associated with a local chronic irritation, such as seen in women who wear a diaphragm or pessary, and in women with cervical neoplasia. However, in most cases, there is no known cause.

Microscopically, the whitish plaque corresponds to the presence of a thick keratin layer (hyperkeratosis) which may or may not contain pyknotic nuclei (parakeratosis) (Figs. 30 and 31). The epithelium is often acanthotic and has a well-developed granular layer, prominent intercellular bridges, and elongated rete pegs. Characteristically, the epithelial cells contain sparse glycogen, but cytological atypia is absent. Frequently, there is epithelial hyperplasia and chronic inflammation. Mature squamous metaplasia is often associated with parakeratosis.

Although there is neither morphological nor clinical evidence that hyperkeratosis and parakeratosis represent precursor lesions to cervical neoplasia, both of these can occur in association with HSIL and invasive cervical cancer. Because of this association, some experts have suggested that all women with otherwise negative Pap smears but demonstrating these findings need colposcopy. However, several studies have reported that less than 4% of women with hyperkeratosis or parakeratosis without nuclear atypia on an otherwise negative Pap smear had HSIL and that in all instances with a squamous intraepithelial lesion it was low-grade. This suggests that routine colposcopic evaluation is unnecessary in such women (Johnson et al. 1991). It should be emphasized, however, that since hyperkeratosis may occasionally overlie HSIL and invasive carcinomas, all grossly visible white plaques on the portio vaginalis or vaginal epithelium should be biopsied.

Noninfectious Cervicitis

Noninfectious cervicitis is, for the most part, chemical or mechanical in nature, and the inflammatory response is nonspecific. Common causes include chemical irritation secondary to douching or local trauma produced by foreign bodies, including tampons, diaphragms, pessaries, and intrauterine contraceptive devices. Surgical instrumentation and therapeutic intervention are common iatrogenic causes of cervical tissue injury and inflammation. Stromal edema, vascular congestion, and neutrophilic infiltration of the

stroma and epithelium characterize acute cervicitis. Clinically, the cervix appears swollen, erythematous, and friable, and there may be an associated purulent endocervical discharge. Prolonged or severe acute inflammation eventually leads to degenerative changes in the epithelial surface, loss of endocervical secretory activity, and ulceration.

In chronic cervicitis, round cells, including lymphocytes, plasma cells, and histiocytes, predominate in the inflammatory infiltrate and are associated with varying amounts of granulation tissue and stromal fibrosis. The diagnosis of chronic cervicitis should be reserved for cases where there is definite clinical and histological evidence of a significant chronic inflammatory process. Otherwise, a histological diagnosis based on the presence of scattered lymphocytes has no clinical significance and is meaningless. Occasionally, lymphoid follicles with germinal centers are found beneath the epithelium in noninfectious cervicitis (Fig. 32). The presence of lymphoid follicles beneath the cervical epithelium is frequently referred to as *follicular cervicitis.* In some instances, the lymphoid inflammatory reactions may produce lymphoma-like lesions, raising the question of lymphoma (see below).

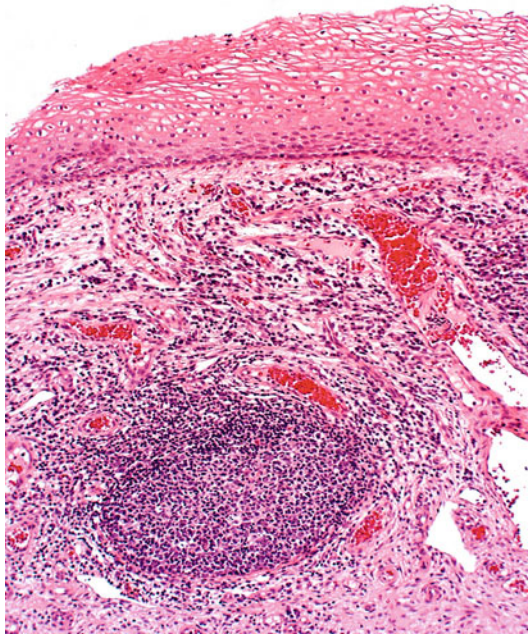

Fig. 32 Chronic cervicitis. A subepithelial lymphoid follicle with a prominent germinal center is present. When lymphoid follicles are numerous, the condition is referred to as *follicular cervicitis*

Infectious Cervicitis

Table 2 summarizes some of the important or pathologically significant etiologic organisms of infectious cervicitis. It is apparent from this listing that infectious cervicitis is important because of its epidemic proportions and because of its central role in the pathogenesis of pelvic inflammatory disease and endometrial infections. According to the understanding of the pathogenesis of pelvic inflammatory disease, infectious cervicitis is the initial event of the pelvic inflammatory disease. It is also the primary infectious focus in related syndromes, such as postpartum and postabortal endometritis. Spontaneous abortion, premature delivery, chorioamnionitis, stillbirth, and neonatal pneumonia and septicemia have been directly related to concurrent bacterial infection of the cervix. Even when asymptomatic, infectious cervicitis can be clinically important since it can act

Table 2 Microorganisms causing infectious cervicitis

Bacteria, chlamydia, mycobacteria, Polymicrobial, endogenous vaginal aerobes, and anaerobes
Chlamydia trachomatis
Neisseria gonorrhoeae
Mycoplasma hominis
Group B *Streptococcus*
Ureaplasma ureolyticum
Gardnerella vaginalis
Actinomyces israelii
Mycobacterium tuberculosis
Treponema pallidum
Viruses
Herpes simplex virus
Human papillomavirus
Fungi
Candida
Aspergillus
Protozoa and parasites
Trichomonas vaginalis
Ameba
Schistosomes

as a source for sexual transmission to male partners, as well as ascending infection in the female, and vertical transmission during pregnancy.

Infectious cervicitis can affect either the endocervical-type columnar epithelium producing *endocervicitis* (mucopurulent cervicitis) or affect the stratified squamous epithelium of the exocervix producing *exocervicitis* (Holmes and Stamm 1999). The infectious agents that cause endo- and exocervicitis tend to differ, although some agents can cause both.

Bacterial and Chlamydial Cervicitis

Bacterial and chlamydial infections of the cervix are the most common cause of infectious cervicitis and are associated with a nonspecific inflammatory response. The columnar epithelium of the endocervix is much more susceptible to bacterial and chlamydial infections than is the surrounding squamous epithelium, and endocervicitis is characteristic. The infectious agents that most commonly cause clinically significant endocervicitis are *Chlamydia trachomatis* and *Neisseria gonorrhoea.* Infection with either of these two agents requires no predisposing factors and is primarily dependent on exposure and size of the inoculum.

Histologically, follicular cervicitis is frequently found in patients with *chlamydia trachomatis* infection and *chlamydia trachomatis* is now presumed to be a major cause of this condition in younger women. *Chlamydia trachomatis* cervicitis has also been associated with a dense, diffuse inflammatory exudate as well as reactive squamous and endocervical atypia (Crum et al. 1984).

Actinomycosis

Actinomyces israelii is a frequent commensual organism found in the female lower genital tract. Culture and immunofluorescence studies of cervical and vaginal secretions indicate that 3–27% of asymptomatic women without obvious risk factors are infected with *actinomyces israelii* (Lippes 1999). Aggregates of bacteria with the morphological appearance of actinomyces have been reported to occur in approximately 0.13% of all Papanicolaou smears (Petitti et al. 1983). The organism is more commonly identified in women with intrauterine devices (IUDs) than in women in the general population, and detection is related to the length of time that the IUD has been in place (Lippes 1999; Petitti et al. 1983; Curtis and Pine 1981). Structures resembling the "sulfur granules" observed in *Actinomyces israelii* infections are sometimes identified in endocervical curettings of asymptomatic women. In the majority of cases, these are "pseudoactinomycotic radiate granules" which are nonspecific collections of bacteria or foreign material (e.g., fragments from nylon strings of IUD), glycoproteins, and lipids rather than actual collections of *Actinomyces israelii* (Bhagavan et al. 1982). The pseudoactinomycotic radiate granules can be distinguished histologically from actinomycotic granules. On H&E stained sections, the actinomycotic granules appear as distinct granules with basophilic peripheral radiating filaments and a dense central eosinophilic core. In contrast, on H&E, the pseudoactinomycotic radiate granules have refractile granules with irregular club-like peripheral projections and no central dense core. The filaments of actinomycotic granules are Gram positive and stain with Gomori methenamine silver stain (GMS). In contrast, the pseudoactinomycotic radiate granules show negative or nonspecific staining with Gram and GMS (Pritt et al. 2006). However, cases that include both pseudoactinomycotic radiate granules as well as true actinomycotic granules have been reported (Boyle and McCluggage 2009).

The identification of *Actinomyces israelii* in asymptomatic women has little clinical significance and does not warrant antibiotic therapy (Lippes 1999). Rarely, *Actinomyces israelii* can be associated with pelvic abscesses.

Tuberculosis

Tuberculosis of the cervix is almost invariably secondary to tuberculous salpingitis and endometritis and is typically associated with pulmonary tuberculosis (see ▶ Chaps. 7, "Benign Diseases of the Endometrium," and ▶ 11, "Diseases of the Fallopian Tube and Paratubal Region"). The prevalence of cervical tuberculosis is difficult to know since it is usually incidentally diagnosed in women undergoing infertility workup. In

women, genital tuberculosis represents about 5–10% of nonpulmonary cases and most of these involve either the endometrium or fallopian tubes (Pintos-Pascual et al. 2017). Cervical involvement only occurs in about 5–15% of cases of genital tuberculosis which means it is diagnosed in only 0.1–0.65% of women with tuberculosis (Sharma 2015). Macroscopically, the cervix may appear normal and inflamed or simulates invasive carcinoma (Pintos-Pascual et al. 2017). Histologically, tuberculous infection of the cervix is recognized by the presence of multiple granulomas or tubercles characterized by central caseous necrosis, epithelioid histiocytes, and multinucleated Langhans giant cells. Granulomas typically disappear after successful antitubercular therapy (Agarwal and Gupta 1993). Tuberculous cervicitis may appear as a noncaseating, granulomatous lesion. Since caseating, nontuberculous granulomas due to lymphogranuloma venereum or sarcoidosis may be encountered in the cervix, the unequivocal diagnosis of tuberculous cervicitis requires demonstration of acid-fast *Mycobacterium tuberculosis*, a straight, rod-shaped bacillus, by Ziehl-Neelsen-stained sections, or by culture (Evans et al. 1984). Because culture yields far better results than staining of tissue sections, unfixed biopsy material should be obtained for microbiologic testing whenever tuberculosis is suspected. The most common granulomatous lesions to be distinguished from tuberculous cervicitis include foreign body giant cell granulomas secondary to sutures, crystals, or cotton, lymphogranuloma venereum, schistosomiasis, and sarcoidosis. Cervical granuloma may occasionally develop after a biopsy or operation as a reaction to local tissue necrosis (Evans et al. 1984).

Other Granulomatous Infections

Certain venereally-transmitted diseases commonly encountered in the vulva may also involve the cervix (see ▶ Chap. 1, "Benign Diseases of the Vulva"). These include syphilis, either as the primary chancre, secondary mucous patches, or tertiary gumma, lymphogranuloma venereum, granuloma inguinale, and chancroid. All these conditions may resemble carcinoma clinically. This is particularly a problem with granuloma inguinale that is endemic in areas of Africa that have high prevalence of invasive cervical cancer. Up to 50% of women with granuloma inguinale may be initially misdiagnosed as having carcinoma of the cervix. Many of these women are thought to have high-stage tumors because of spread of the infection to the parametrial tissue (Hoosen et al. 1990). In addition to characteristic morphologic features, specific bacteriologic and immunologic techniques are available for identifying each of these diseases.

Viral Diseases

In contrast to bacterial infections of the cervix, the most common cervical viral infections – HPV and herpes simplex virus (HSV) – have a predilection for the squamous epithelium and produce characteristic morphologic changes. Cytomegalovirus, although often isolated from cervical secretions, is not typically associated with cervicitis, and its role in cervical infection is poorly understood.

Herpes simplex virus (HSV) Infection

Although the precise prevalence of cervical HSV infection (herpes genitalis) is not known, it is far greater than generally recognized. At least 50 million individuals in the US have genital HSV infection (Workowski and Berman 2006). Up to 70% of HSV-2 infections appear to be asymptomatic. Both HSV-1 and HSV-2 can cause genital herpes, and in some populations, HSV-1 is more common as the cause of initial herpes infection than is HSV-2 (Workowski and Berman 2006). However, HSV-2 is responsible for the majority of cases of recurrent HSV. Cervical involvement can be detected in 70–90% of women with primary genital HSV-2 infections. Occasionally, in women with cervical involvement, the ulceronecrotic process is so extensive that a fungating, necrotic mass appears on the cervical portio, which can be mistaken for carcinoma. During the vesicular phase of a cervical lesion, a biopsy may reveal the presence of suprabasal intraepidermal vesicles filled with serum, degenerated epidermal cells, and multinucleated giant cells, some containing eosinophilic, intranuclear inclusions surrounded by a clear halo (Fig. 33).

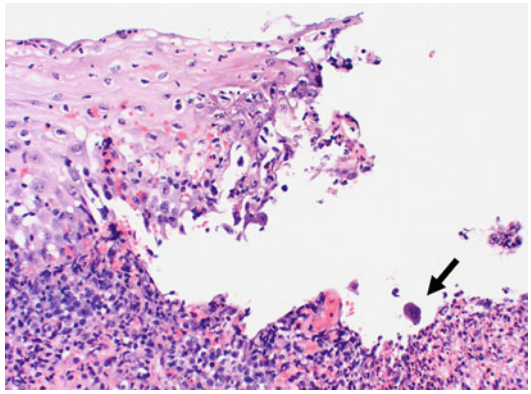

Fig. 33 Herpetic cervicitis. Suprabasal vesicle in squamous epithelium of the portio. A multinucleated squamous cell with a ground-glass intranuclear viral inclusion is present in the lower right

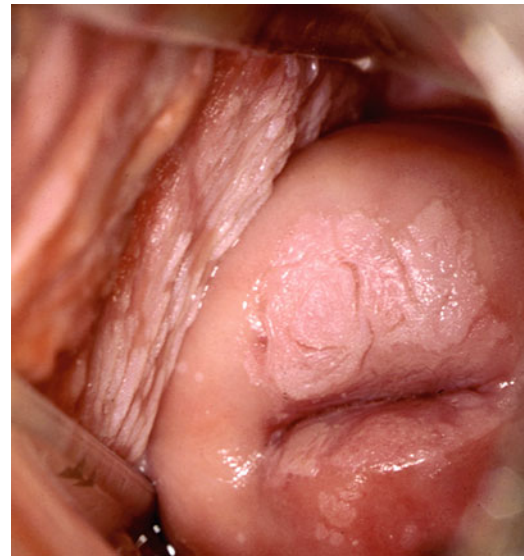

Fig. 34 Exophytic condyloma acuminata The lesions are multifocal and form raised white papillary projections on both the vagina and cervix

Herpes-Like Lesions

Vesicular and bullous lesions of the cervical squamous mucous membrane, other than herpetic cervicitis, have been reported (Burd and Easterly 1971). Pemphigus vulgaris of the cervix is a common finding in women with generalized disease (Kaufman et al. 1969). Microscopically, there are multiple intraepithelial bullae in a suprabasal location containing the characteristic acantholytic Tzanck cells.

Human Papillomavirus (HPV)

The College of American Pathologists (CAP) – American Society of Collposcopy and Cervical Pathology LAST Project recommended that exophytic condyloma acuminata be designated as LSIL and allow for the additional optional designation of condyloma in parenthesis (Darragh et al. 2012). Exophytic LSIL (condyloma) are one of the common manifestations of HPV type infection of the lower anogenital tract and are usually caused by HPV type 6 and less frequently type 11 (Sugase et al. 1991). Exophytic LSIL (condylomas) are quite common on the vulva and perianal region and less common on the cervix. When florid exophytic LSIL (condyloma) of the vulva are identified, multicentric disease can occur and internal vaginal or cervical exophytic condylomas can be occasionally identified. Exophytic LSIL (condyloma) of the cervix without vulvovaginal involvement is rare. They are commonly multifocal and may involve the mature squamous epithelium of the native cervical portio as well as the immature squamous epithelium of the transformation zone, including metaplastic squamous epithelium replacing endocervical glands. Extension into the endocervical canal may occur. Grossly and colposcopically, exophytic LSIL (condyloma) appear white, and the degree of whiteness depends largely on the thickness of associated surface hyperkeratosis (Fig. 34). Other configurations of cervical exophytic LSIL (condyloma) include a myriad of minute, maculopapular, only slightly raised, areas involving the vagina and the cervix.

Microscopically, the histological features of exophytic LSIL (condyloma) include architectural alterations such as papillomatosis, acanthosis, parakeratosis, and hyperkeratosis, as well as cytologic alterations including koilocytosis (manifested by perinuclear cytoplasmic cavitation), nuclear enlargement and atypia. Multinucleation is also frequently observed (Fig. 35).

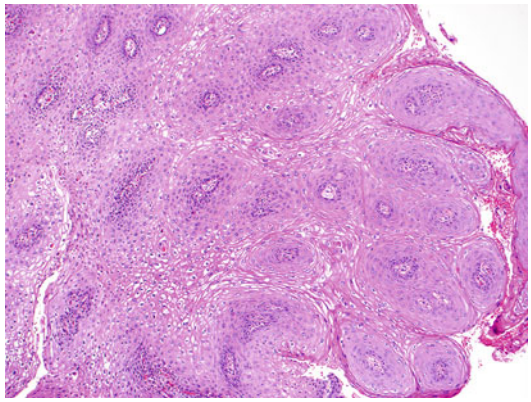

Fig. 35 Exophytic LSIL (condyloma). The classic histological features are papillomatosis with acanthosis, parakeratosis, hyperkeratosis, as well as cytological alterations including multinucleation, koilocytosis, and nuclear atypia

The natural history of exophytic LSIL (condyloma) is one of spontaneous regression, good response to conservative therapy, unpredictable recurrence, and sometimes persistence. Lesion regression or apparent cure following biopsy is fairly common. The natural history of exophytic LSIL (condyloma) in general may be modified by host factors, notably immunosuppression and steroid hormone levels.

Fungal Diseases

Cervical fungal infection by *Candida albicans* usually occurs as part of a generalized lower genital tract infection involving the vagina and vulva. Antibiotic therapy, poorly controlled diabetes mellitus, and immunosuppression all favor fungal overgrowth (Sobel 1997). Cervical candidal infections can be associated with increased numbers of polymorpholeukocytes present in the upper layers of the epithelium and fungal hyphae that can be identified by PAS stains both at the surface of the epithelium and within the superficial layers of the epithelium.

Protozoal and Parasitic Diseases

Cervical infestation by *trichomonas vaginalis* is quite frequent and most often associated with concurrent trichomonal vaginitis. Acute trichomonal cervicitis may provoke an intense inflammatory response with prominent reparative atypia in exfoliated squamous and endocervical cells, with corresponding gross and colposcopic abnormalities.

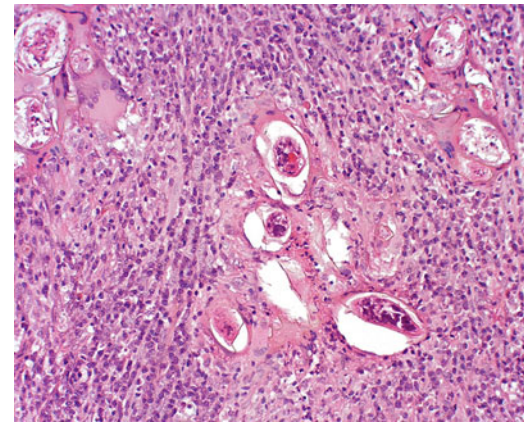

Fig. 36 Cervical schistosomiasis. Note calcified *Schistosoma haematobiium* ova

Rare instances of parasitic infestations, such as echinococcosis or hydatid cysts, Chagas' disease, and ulceronecrotic amebiasis have been encountered in the cervix (Concetti et al. 2000). In contrast, schistosomiasis (bilharziasis) of the cervix, generally caused by *Schistosoma mansoni*, is very common in Africa (Egypt), South America, Puerto Rico, and several Asian countries (Rand and Lowe 1998). A large number of cases of cervical schistosomiasis are associated with urinary schistosomiasis and sterility. Microscopically, noncaseating granulomas (pseudotubercles) with ova surrounded by multinucleated giant cells are seen and the ova are often calcified (Fig. 36). *S. mansoni* has a long lateral spine, whereas *S. haematobium* has a short spine extending from one of its poles. Cervical schistosomiasis may be associated with extensive pseudoepitheliomatous hyperplasia of the cervical squamous epithelium, masquerading both clinically and histologically as carcinoma. Although it was previously thought that chronic, untreated cervical schistosomiasis plays a role in the genesis of cervical carcinoma in populations where schistosomiasis is prevalent, there is now evidence indicating no association between schistosomiasis and cervical cancer (Riffenburgh et al. 1997).

Cervicovaginitis Emphysematosa

Multiple, blue-gray, subepithelial cysts of the portio vaginalis and vagina characterize this unusual disease (Gardner and Fernet 1964). In rare cases, the cysts have been misdiagnosed as an invasive cervical cancer (Akang et al. 1997).

The cause of this condition is unknown, but it is often associated with trichomoniasis (Gardner and Fernet 1964). Gas-forming bacteria have never been identified within the cysts. The cysts are dilated connective tissue spaces without lining epithelium that contain air and carbon dioxide. Multinucleated foreign body giant cells surround some of the cysts, and often the subepithelial veins and lymphatics are dilated.

Cervical Vasculitis

Gynecologic vasculitides are rare conditions occurring in between 0.04% and 0.1% of surgically removed gynecologic specimens. Most are isolated, single-organ disease and the cervix is the most frequently involved organ (Hernandez-Rodriguez et al. 2009). Single-organ vasculitis or "isolated" arteritis of the cervix, is histologically identical but clinically unrelated to polyarteritis nodosa (Laurtizen and Meinecke 1987; Gozukucuk et al. 2016; Ganesan et al. 2000). In most cases, medium-sized arteries contain nongranulomatous vasculitis which is usually asymptomatic and identified as an incidental finding in surgical specimens. Occasionally, it may be associated with bleeding and a few cases have clinically resembled cancer. The etiology of this condition is unknown. A literature review done in 2007 identified 118 cases of single organ vasculitis of the cervix and found that 99.1% were nonprogressive to systemic disease and that excision of the tissue appeared to be curative (Hoppe et al. 2007). Therefore, if no systemic disease is identified, no further therapy is indicated.

Pseudoneoplastic Glandular Conditions (Hyperplasias) and Endometriosis

Microglandular Endocervical Hyperplasia

Microglandular endocervical hyperplasia is a benign proliferation of endocervical glands. Microglandular hyperplasia is frequently detected as an incidental finding on a cervical biopsy, cone biopsy, or a hysterectomy specimen. It has been detected in up to 27% of cone biopsies or hysterectomy specimens (Brown and Wells 1986). It appears to arise from reserve cells derived from columnar cells (Witkiewicz et al. 2005). If clinically apparent, it most often resembles a cervical polyp measuring 1–2 cm in size. Patients may complain of postcoital bleeding or spotting. Microglandular hyperplasia is most common in women of reproductive ages although some cases (<10%) occur in postmenopausal women (Nucci 2014). Early studies reported that microglandular hyperplasia typically occurs in patients with a history of recent progesterone exposure, either as a result of oral contraceptive use or pregnancy, and concluded that it represents a progestin-induced lesion. However, a number of cases have been reported in which there is no associated hormonal history, and a comprehensive study did not find a relationship between microglandular hyperplasia and progestin exposure (Greeley et al. 1995). Therefore, the role of progestin exposure in the pathogenesis of this lesion is currently unclear.

Histologically, microglandular hyperplasia may present in a single focus or be distributed in multiple foci. It may involve the surface and/or deeper portions of endocervical clefts. The most common form consists of tightly packed varying-sized glandular or tubular units lined by flattened to cuboidal cells with eosinophilic granular cytoplasm containing small quantities of mucin (Fig. 37a, b). The glands vary in size and shape from round and small to large irregularly dilated cystic structures. The stroma separating the glands is usually infiltrated with acute and chronic inflammatory cells. The nuclei of the endocervical cells are uniform, with occasional pleomorphism and hyperchromasia, but mitotic activity is quite low with only 1 mitotic figure per 10 high-power fields (Young and Scully 1989). Associated squamous metaplasia and subcolumnar reserve cell hyperplasia are seen in a large number of cases. Foci with a solid proliferation of cells, including signet ring cells, can also be present. In more florid forms of microglandular hyperplasia, the glandular elements are arranged in a reticulated or solid pattern with areas of nuclear hyperchromasia and pleomorphism. The significance of the florid forms of microglandular hyperplasia is that the irregularly arranged glands can impart an infiltrative appearance and they can be mistaken for adenocarcinoma; in particular, clear cell adenocarcinoma.

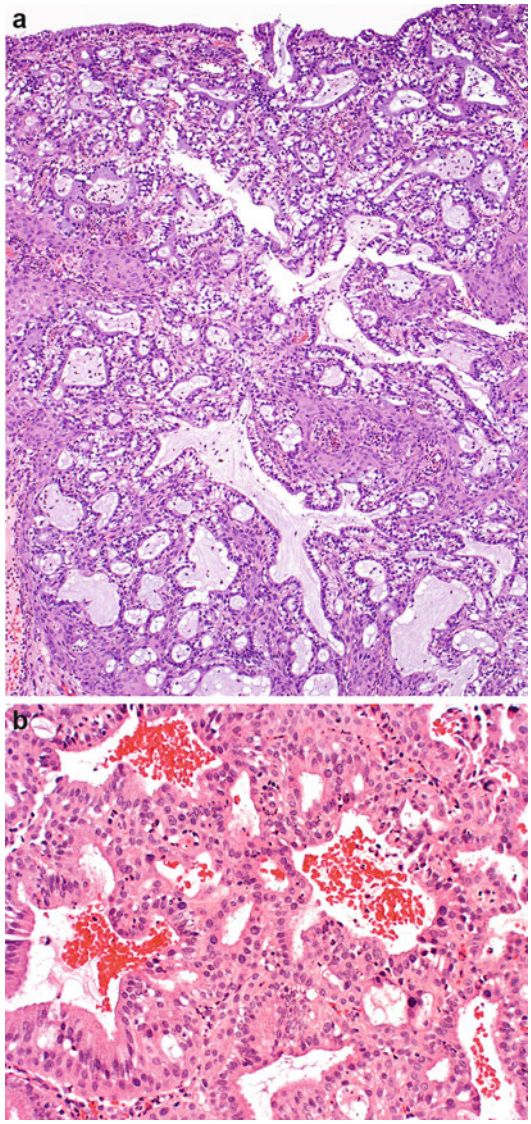

Fig. 37 Microglandular hyperplasia. (**a**) There is an adenomatous pattern with cuboidal lining cells and focal squamous metaplasia. (**b**) At higher magnification, the cells appear quite uniform and form a reticular pattern. Note the extensive vacuolization of the lesion that is caused by cystic dilation of intercellular spaces. There is a paucity of intracellular mucin

Microglandular hyperplasia with solid areas, especially when the solid component predominates or when signet ring cells are present, can also be difficult to distinguish from adenocarcinomas (Young and Scully 1989). The benign nature of these florid lesions is usually demonstrable by a lack of clear-cut stromal invasion and the low mitotic activity of microglandular hyperplasia as compared to endocervical adenocarcinoma. In addition, florid forms of microglandular hyperplasia almost always contain areas with the more typical histological features of microglandular hyperplasia. In older women, it is important to distinguish microglandular hyperplasia from "microglandular hyperplasia-like" endometrial carcinomas. This is particularly a problem when there are only small fragments of an endometrial tumor present in an endocervical curettage or alternatively when fragments of microglandular hyperplasia are present in an endometrial biopsy or curettage. Histological features that favor an endometrial carcinoma are continuity with clearly identifiable endometrium, presence of foamy macrophages in the stroma, and more cytological atypia and mitotic activity than typically seen with microglandular hyperplasia.

The immunohistochemical profile of microglandular hyperplasia includes p63 positivity in the associated squamous metaplasia and reserve cell component (Chekmareva et al. 2008; Houghton and McCluggage 2009). Microglandular hyperplasia is usually positive for ER and PR and may show luminal positivity for carcinoembryonic antigen (CEA) (Qiu and Mittal 2003). It is usually vimentin negative which may be useful for distinguishing microglandular hyperplasia from an endometrial carcinoma (Qiu and Mittal 2003). (see ▶ Chap. 6, "Carcinoma and Other Tumors of the Cervix") discusses the use of immunohistochemistry in the differential diagnosis of endocervical and endometrial lesions.

Mesonephric Hyperplasia and Remnants

The vestigial elements of the distal ends of the mesonephric ducts are found in 1–22% of adult cervices and in up to 40% of the cervices of newborns and children (Huffman 1948; Sneeden 1958). The wide variation in the reported prevalence of these remnants appears to be a function of how extensively the cervix is sampled and the site of sampling (Ferry and Scully 1990). Mesonephric remnants are most commonly present in the lateral aspects of the cervix, a region that is

usually not sampled on routine hysterectomy specimens. They consist of small tubules or cysts that are usually located deep in the lateral cervical wall. Characteristically, the tubules are arranged in small clusters or have an orderly distribution reminiscent of the ampullary portion of the fetal mesonephric duct. The tubules are lined by nonciliated, low columnar, or cuboidal epithelium. The lining cells contain no glycogen or mucin, features that distinguish mesonephric from endocervical epithelium (Fig. 38). The tubular lumen, however, is often filled with pink, homogeneous, PAS-positive secretions.

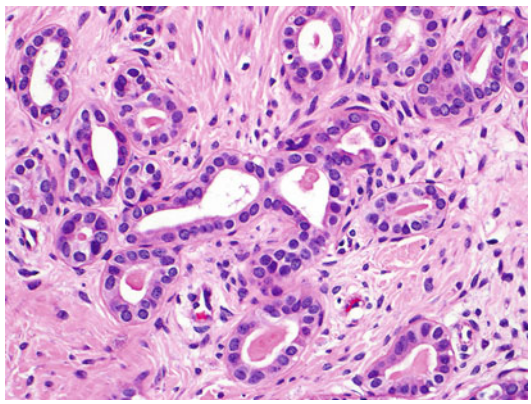

Fig. 38 Mesonephric remnants. The mesonephric tubules are lined by cuboidal epithelium with bland nuclei. Occasional tubules contain pink, homogenoeous intraluminal secretions

Mesonephric remnants may become hyperplastic, resulting in a florid, tubuloglandular proliferation with transmural involvement of the cervix (Fig. 39). Based on the architecture of the glandular structures, mesonephric hyperplasia has been classified by some authors into different histological types (Ferry and Scully 1990; Seidman and Tavassoli 1995). The most common type is called the lobular type and is characterized by clustered mesonephric tubules, with or without a centrally placed duct. The lobular form tends to occur at a younger age, is less extensive, and tends to arise deeper in the cervical stroma. The less common type is called the diffuse type and is characterized by a nonclustered diffuse pattern or proliferation of mesonephric tubules. The histological subdivision of mesonephric hyperplasia into different forms does not have clinical significance.

Mesonephric hyperplasia is almost always asymptomatic and is detected on either cervical biopsy, cone biopsy, or hysterectomy specimens. Histological differentiation between mesonephric hyperplasia and mesonephric remnants is quite arbitrary, and of little clinical importance. Mesonephric hyperplasia is a benign condition that is of pathological significance because it can be misinterpreted as a minimal deviation adenocarcinoma of the endocervix. Mesonephric hyperplasia is usually

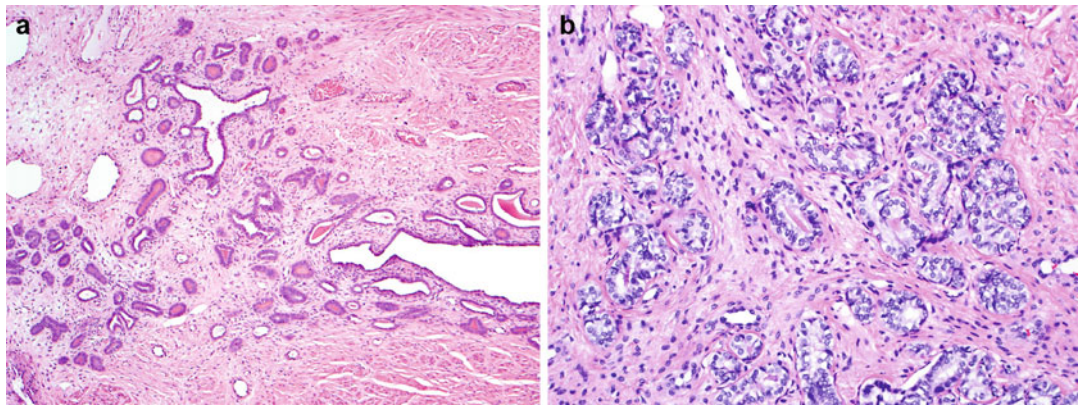

Fig. 39 Florid mesonephric hyperplasia. (**a**) Extensive mesonephric tubular-ductal proliferation in the deeper portion of the cervix, resembling an invasive adenocarcinoma. Unlike the latter, the lobular architecture is maintained in hyperplasia. Note the mesonephric duct in center surrounded by a proliferation of small tubules. (**b**) The gland lumens can retain pink-homogeneous intraluminal secretions. The cells resemble the cells of mesonephric remnants

distinguished from the rare mesonephric adenocarcinoma by lack of a complex glandular pattern, mitosis, intracellular mucin, and periglandular stromal edema; however, some florid forms of hyperplasia can be problematic to distinguish from carcinoma. The most useful immunohistochemical markers for distinction of mesonephric hyperplasia (and adenocarcinoma) from endocervical and endometrial adenocarcinomas depend on the specific type of adenocarcinoma that is being considered. Mesonephric lesions lack diffuse p16 expression and also hormone receptor expression (ER/PR) but have a high frequency of GATA-3 expression. Thus all these markers are useful for distinction of mesonephric lesions from endometrial endometrioid carcinomas but only p16 and GATA-3 are useful for distinction from high-risk HPV-related endocervical adenocarcinomas and only GATA-3 is useful for distinction from gastric-type (non-HPV) endocervical adenocarcinomas (Roma et al. 2015; Howitt et al. 2015).

Lobular Endocervical Glandular Hyperplasia (LEGH)

Endocervical hyperplasia can sometimes be encountered and can take several different forms. LEGH is a rare form, first described by Nucci et al. (Nucci et al. 1999). Later studies have shown that it has a distinctive gastric phenotype (pyloric gland metaplasia) by demonstrating immunohistochemical positivity for H1K1083, an antibody specific for gastric pyloric mucin (Mikami et al. 2009). Most cases are incidental findings in hysterectomy specimens; some patients, however, complain of abundant mucoid or watery discharge. Microscopically, there is a proliferation of tightly packed, small-sized endocervical glands displaying a well-demarcated, multilobular pattern. Several of the lobules are centered by a larger glandular structure (Fig. 40a, b). Typically, LEGH is confined to the inner one-half of the cervical wall, and the gland-lining cells lack significant atypia and have a low mitotic index. LEGH may be mistaken for well-differentiated endocervical adenocarcinoma (minimal deviation adenocarcinoma/adenoma malignum) (see ► "Carcinoma and Other Tumors of the Cervix"). The orderly, lobular architecture of glandular units, absence of irregular, deep stromal infiltration and desmoplasia, and the lack of distinctive nuclear atypia are features distinguishing the former from the latter. An atypical form of LEGH has been recognized as a potential link/precursor lesion between LEGH and gastric-type/minimal deviation adenocarcinoma (chromosomal imbalances common in minimal deviation adenocarcinomas have been identified in some cases) (Kawauchi et al. 2008).

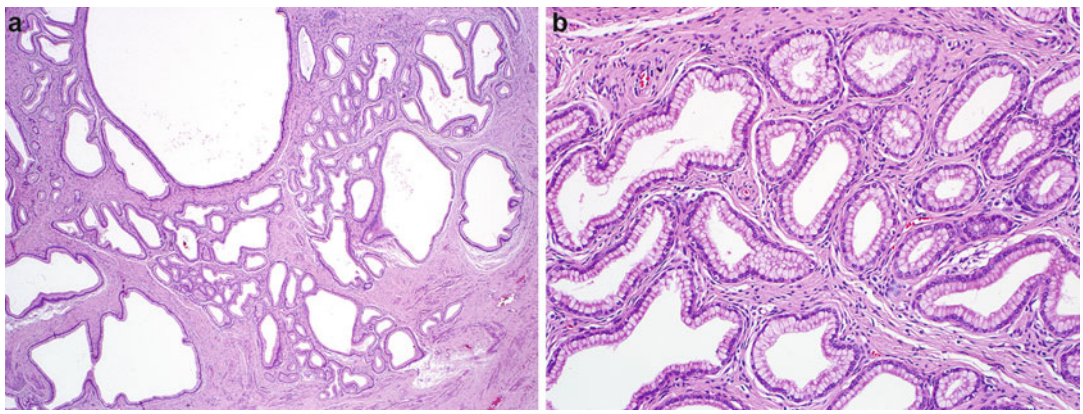

Fig. 40 LEGH (**a**) There is a proliferation of highly packed, small-sized endocervical glands in a lobular pattern. (**b**) The glands lack nuclear atypia and resemble gastric pyloric-type epithelium

Atypical LEGH has atypical architectural and cytological features, including nuclear enlargement, irregular nuclear contour, distinct nucleoli, coarse chromatin texture, loss of polarity, occasional mitotic figures, apoptotic bodies and/or nuclear debris in the lumen, and infolding of epithelium or papillary projections with fine fibrovascular stroma (Mikami et al. 2004).

Diffuse Laminar Endocervical Glandular Hyperplasia (DLEGH)

DLEGH is another rare form of hyperplasia described by Jones et al (Jones et al. 1991) in which tightly packed, small-to-medium-sized endocervical glands are typically confined to the upper one-third of the cervical wall (Fig. 41a, b). Unlike LEGH, its laminar counterpart is devoid of lobulation and is clearly demarcated from the underlying stroma exhibiting a straight line at its base. The lining epithelium of glandular structures is cytologically normal without mitoses, and stromal desmoplasia is not seen. These features and its superficial position distinguish DLEGH from gastric-type/minimal deviation endocervical adenocarcinoma (adenoma malignum).

Occasionally, cases of endocervical hyperplasia are encountered which do not fit the published descriptions of either LEGH or DLEGH. The descriptive term *endocervical hyperplasia – NOS* is used to describe such cases. Fig. 42a, b illustrates such a case which lacks both a lobular architecture and a well-demarcated laminar architecture. Follow-up studies of such lesions are not published, but most cases are diagnosed on hysterectomy specimens and appear to be incidental findings.

Endocervicosis

Endocervicosis is a very rare condition in which the outer aspect of the cervical wall is enlarged, rubbery, and may be grossly cystic (Zaino 2000; Young and Clement 2000). Histologically, glands varying in shape and size, often cystically dilated, are lined by mucinous-type endocervical cells and typically occupy the outer one-third of the cervical wall with extension to the paracervical tissues (Fig. 43). The lining epithelium is normal to flattened with very occasional mitotic figures and occasional glands are surrounded by endometrial-like stroma. Overall, the lesion resembles endocervicosis of urinary bladder and its distinctive feature from adenoma malignum is that it is located in the outer wall of the cervix with

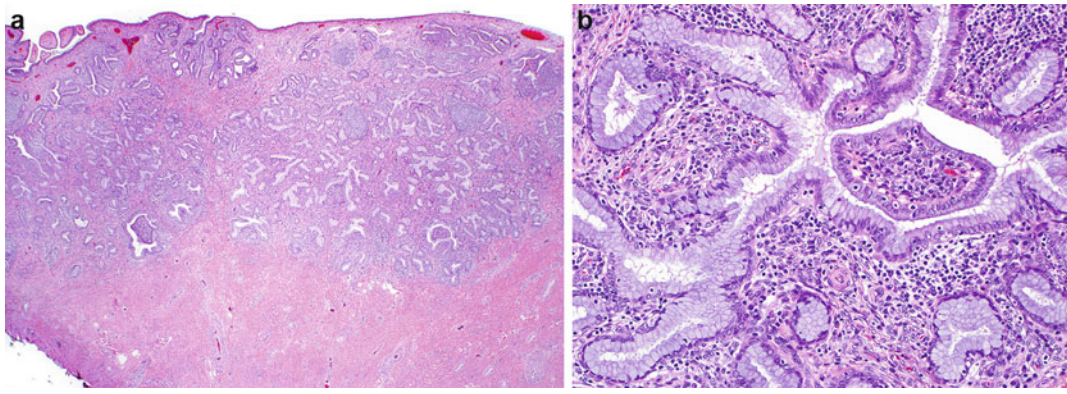

Fig. 41 DLEGH (**a**) There is a proliferation of highly packed, small-sized endocervical glands that is clearly demarcated from the underlying cervical stroma. (**b**) Glandular branching and an inflammatory reaction are present but the cells lack nuclear atypia and have a normal endocervical appearance

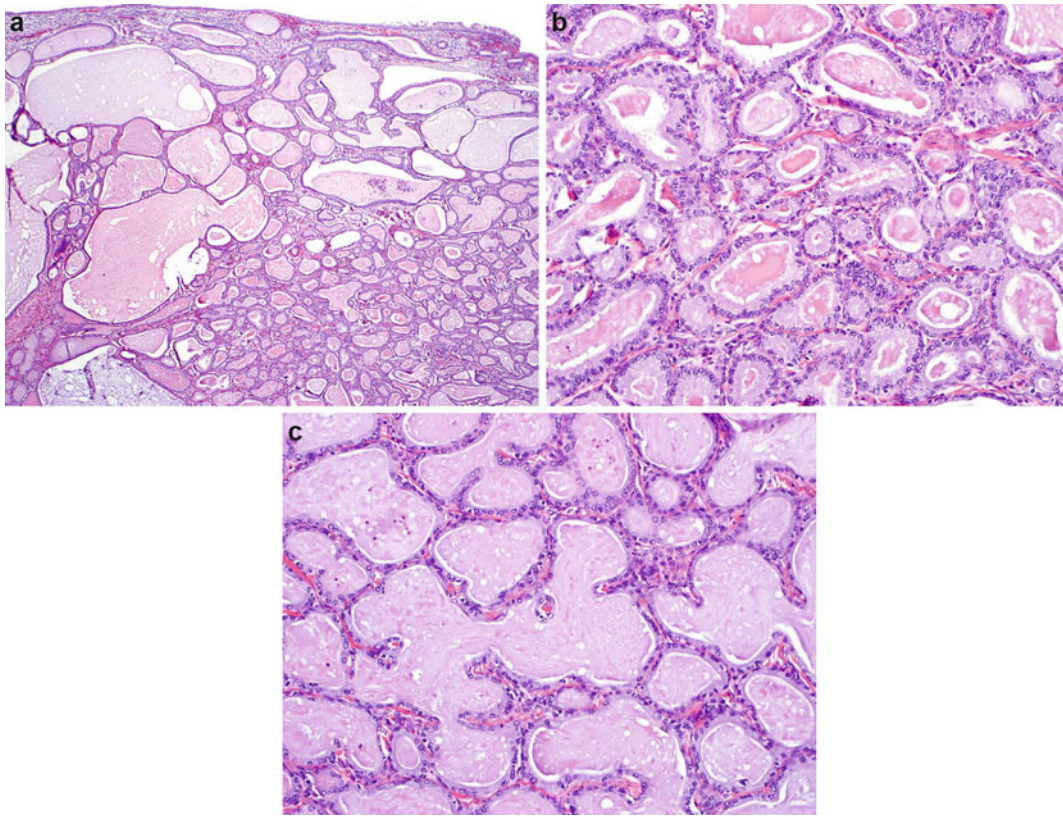

Fig. 42 Endocervical glandular hyperplasia – NOS. (**a**) There is a proliferation of densely packed endocervical glands. (**b**) Rounded glands with columnar cells lack cellular atypia or mitotic activity and there is no stromal reaction to the proliferation. (**c**) Attenuated glands can have irregular, convoluted shapes

clear demarcation from the upper, normal endocervical glands of the endocervical mucosal layer (Young and Clement 2000).

Endometriosis

Endometriosis refers to lesions that are composed of ectopic endometrial glands and stroma, whereas *tubo-endometrioid metaplasia* refers to endocervical glands that are lined by ciliated cells or secretory type cells with apical snouts that resemble those that can be seen in the endometrium but which lack endometrial stroma. Endometriosis of the cervix may occur on the portio or in the endocervical canal. The process is usually confined to the superficial third of the cervical wall (Baker et al. 1999). Most areas of endometriosis of the exocervix appear as one or more, small, blue, or red nodules, measuring a few millimeters in diameter. Occasionally, however, the lesion may be larger or cystic and may produce abnormal vaginal bleeding. Histologically, the glands and stroma resemble proliferative endometrium (Fig. 44). Rarely, the glands are secretory. Decidua may be seen in pregnancy or with progestin therapy.

The mechanism responsible for the development of endometriosis is unknown, but it is clear that cervical endometriosis frequently develops following cervical trauma. Cervical endometriosis is encountered in 5%–43% of patients who have had cervical cautery or cold-knife cone biopsy or loop excisional procedures (Gardner 1966). This association has been interpreted by some investigators as evidence supporting the implantation theory of endometriosis. According to this theory, endometrial tissue is implanted into

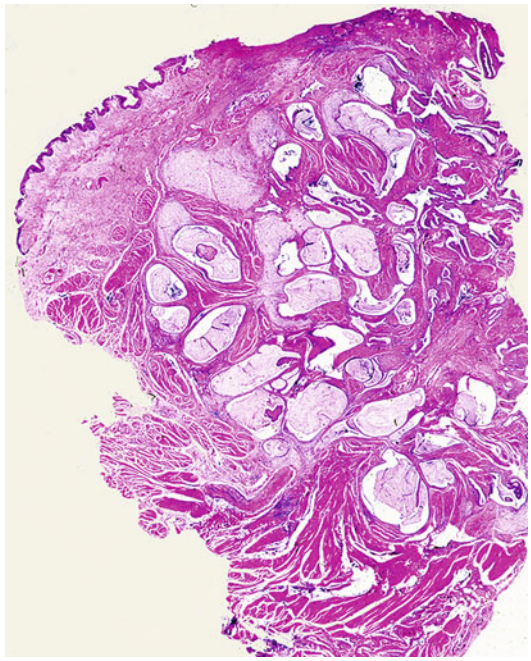

Fig. 43 Endocervicosis of the cervix. Cystically dilated endocervical glands extend into the outer third of the wall of the cervix. (Photograph courtesy of Dr. Phillip Clement of Vancouver, Canada)

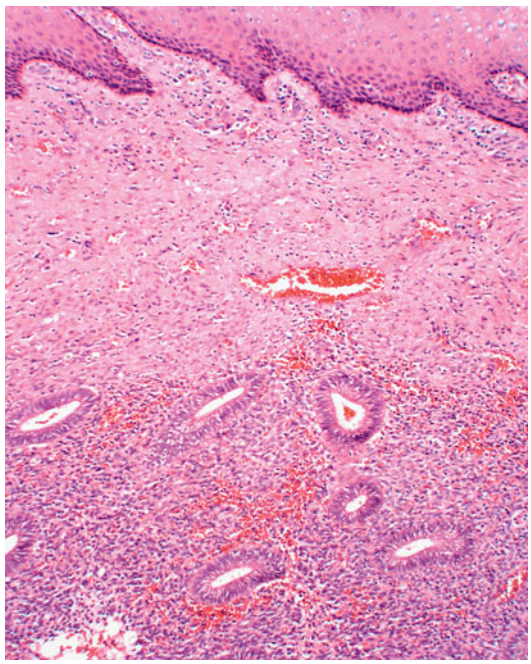

Fig. 44 Endometriosis of the cervix. Both typical endometrial glands and stroma are present beneath the squamous portio epithelium

the cervical mucosa or submucosa following postmenstrual cauterization or during delivery. However, the frequent occurrence of posttraumatic endometriosis could also be interpreted as supporting the view that cervical endometriosis represents a reparative/metaplastic process. Support for the concept that cervical endometriosis develops as a metaplastic process as opposed to direct implantation also comes from the frequent demonstration of glands with either *tuboendometrioid* or pure *tubal metaplasia* in posttraumatic cervices.

Benign Tumors

Endocervical Polyps

Endocervical polyps constitute the most common new growths of the uterine cervix. Cervical polyps are focal, hyperplastic protrusions of endocervical folds, including the epithelium and substantia propria. Cervical polyps are most often found during the fourth to sixth decades and in multigravidas. They may present with profuse leukorrhea due to hypersecretion of mucus from inflamed endocervical epithelium or abnormal bleeding from ulceration of the surface epithelium. Clinically, cervical polyps are rounded or elongated with a smooth or lobulated surface that is often reddened because of increased vascularity. Most polyps are single and measure from a few millimeters to 2–3 cm. In rare instances, they may reach gigantic dimensions, protruding beyond the introitus and resembling carcinoma. Various cervical lesions with a polypoid gross appearance are presented in Table 3. Microscopically, cervical polyps display a variety of patterns that vary according to the preponderance of one or another of the tissue components. The most common type is the endocervical mucosal polyp. It is composed of mucinous epithelium that lines crypts, with or without cystic changes (Fig. 45). Occasionally, they may be mainly fibrous, representing an overgrowth of the connective tissue stroma of the portio. In other cases, blood vessels predominate and the lesion is called a *vascular polyp*. Squamous metaplasia involving

Table 3 Differential clinical diagnosis of polypoid lesions of the cervix

Polyp	Squamous papilloma
Microglandular endocervical hyperplasia	Condyloma acuminatum
Decidua	Papillary adenofibroma
Granulation tissue	Squamous cell carcinoma
Leiomyoma	Adenocarcinoma
Adenomyoma	Sarcoma, primary or secondary
Fibroadenoma	

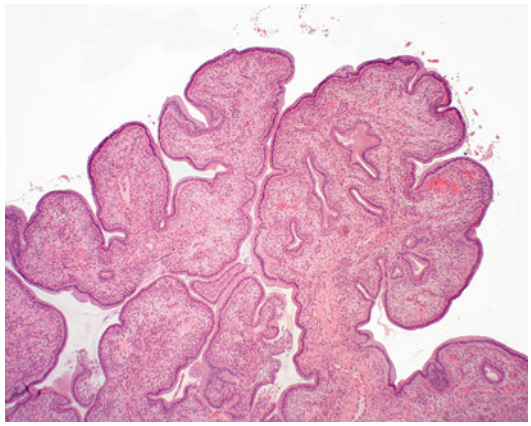

Fig. 45 Endocervical polyp. This is the most common histological type of endocervical polyp. Endocervical-type, tall columnar, mucinous epithelium covers the surface and crypts

the surface or glandular epithelium of polyps is frequently observed. The supporting connective tissue of polyps is generally loose, with centrally placed feeding vessels, and is almost always infiltrated by a chronic inflammatory infiltrate. Occasionally, such infiltration may be so extensive as to be the principal tissue constituent of the polyp. In these cases, polypoid granulation tissue devoid of surface epithelium is observed (Fig. 46). Polyps originating in the isthmus often have an admixture of endocervical- and endometrial-type epithelial components and are referred to as *mixed polyps*.

HSIL, carcinoma, either in situ or invasive (adeno- or squamous), arising in cervical polyps is extremely rare. Endocervical polyps with adenocarcinomatous changes must be differentiated from polypoid adenocarcinoma of the endocervix and

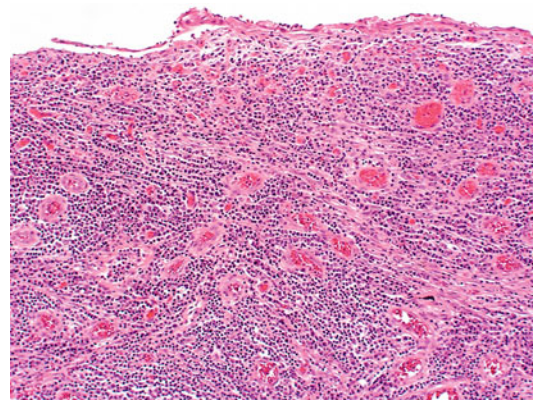

Fig. 46 Granulation tissue. Polypoid nodules of granulation tissue can grossly resemble an endocervical polyp. This type of lesion often leads to bleeding

from endocervical polyps that are secondarily involved by adjacent adenocarcinoma. The most useful criterion for differentiating between the two is to determine whether or not the base of the pedicle of the polyp is involved by carcinoma. The base of a polyp that harbors a primary tumor is free of disease and the carcinoma usually has a focal distribution within an otherwise benign polyp. In a polypoid carcinoma, the entire mass is malignant, including its base and neighboring areas. It is not clear whether a focus of carcinoma in a cervical polyp without involvement of its base but associated with similar carcinoma in the adjacent regions is the primary focus with non-contiguous spread to the non-polyp region or vice versa.

Mesodermal Stromal Polyp

Mesodermal stromal polyps are benign, exophytic proliferations of stroma and epithelium that can occur in the vagina and cervix of women of reproductive ages. These lesions are seen most frequently in pregnant patients and arise more commonly from the vagina than from the cervix (Norris and Taylor 1966). Histologically, these polyps are composed of an edematous stroma that is covered by a benign appearing stratified squamous epithelium (Fig. 47a). The stromal component is usually comprised of bland appearing plump stromal fibroblasts. However, in some cases, there can be focal areas of

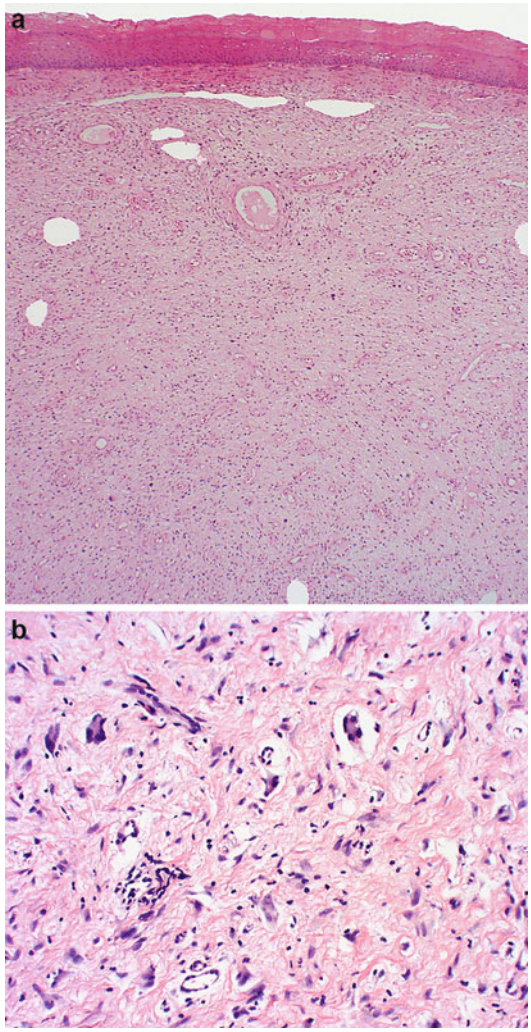

Fig. 47 Mesodermal stromal polyp. (**a**) Spindle-shaped and stellate fibroblasts are embedded in a loose myxoid stroma that has a stratified squamous surface epithelium. (**b**) At higher magnification, stellate atypical fibroblasts can be seen in the stroma

bizarre fibroblasts with irregular, occasionally multinucleated hyperchromatic nuclei that resemble the fibroblasts in radiation reactions (Fig. 47b) (Clement 1985). Occasional multinucleated stromal giant cells can be identified in approximately 25% of cone biopsy or hysterectomy specimens when carefully searched for (Hariri and Ingemanssen 1993). These cells stain negatively for cytokeratin, desmin, factor VIII, and S100 protein, but stain positively for vimentin and alpha1-antichymotrypsin. When stromal polyps contain large numbers of these cells, they can appear quite alarming and simulate the appearance of sarcoma botryoides (Elliott and Elliott 1973). However, careful inspection will allow these lesions to be differentiated from sarcoma botryoides by the absence of mitotic figures, lack of rhabdomyoblasts, and lack of a cambium layer.

Superficial Cervicovaginal Myofibroblastoma

Superficial cervicovaginal myofibroblastoma is an uncommon mesenchymal tumor that is histologically distinguishable from a mesodermal stromal polyp and can be found in the cervix and vagina of adult women (Laskin et al. 2001). They arise from the lamina propria and are located in the subepithelial region. They are well circumscribed and range in size from 1 to 6.5 cm in diameter. Superficial cervicovaginal myofibroblastomas are moderately to highly cellular and composed of bland spindle shaped mesenchymal cells that are surrounded by a collagenous stroma that can have myxoid and edematous foci. Characteristically, they have a multipatterned architecture that can consist of a lacelike/sievelike growth pattern of the mesenchymal cells in areas with more stroma and a fasicular growth pattern in the more cellular regions. Mitotic activity is minimal (Laskin et al. 2001). The cells stain positively for vimentin, ER and PR, desmin and CD 34. Some cases stain for smooth muscle actin and muscle-specific actin.

Placental Site Trophoblastic Nodule

Placental site trophoblastic nodules can be found in the endocervix, immediately beneath the epithelium. They are sometimes detected in endocervical curettages. These lesions are histologically identical to early implantation sites that can be detected in the endometrium of women of reproductive ages (Young et al. 1988). Microscopically, placental site trophoblastic nodules are well-defined lesions that have a hyalinized appearance and contain chorionic-type

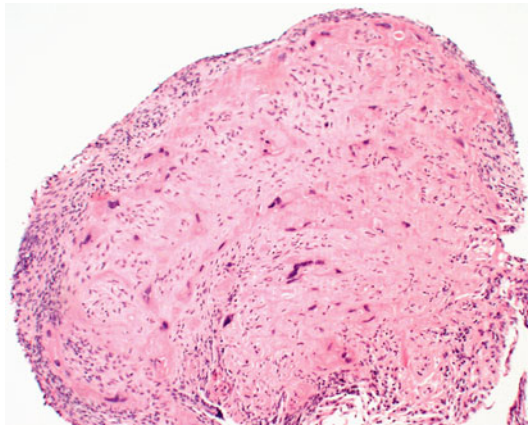

Fig. 48 Placental site trophoblastic nodule. A hyalinized nodule containing intermediate trophoblasts is identified in an endocervical curettage obtained several months postpartum

intermediate trophoblastic cells and inflammatory cells (Fig. 48). The intermediate trophoblastic cells are frequently degenerated and have extensive cytoplasmic vacuolization. They have some variable atypia and can have some central necrosis but have a very low mitotic index and low Ki-67 labeling indices (Shih and Kurman 1998). Intermediate trophoblastic cells of chorionic type stain positively with antibodies against cytokeratins, human placental lactogen (HPL), Mel-CAM, a cell adhesion molecule of the immunoglobulin gene superfamily, and p63 (Shih and Kurman 1998). Lack of significant atypia, low mitotic activity, and lack of diffuse p16 expression assist in distinction from invasive squamous cell carcinomas.

Leiomyoma

Cervical leiomyomas are much less common than uterine leiomyomata. They usually occur singly and produce unilateral enlargement of the cervical portio. At times, the lesion may protrude from the canal, resembling an endocervical polyp, and in pregnancy may produce dystocia. Cervical leiomyomas are similar grossly to those observed in the myometrium; microscopically, they tend to be more vascularized than those of the uterus, a variety of histological patterns may be encountered, including atypical leiomyoma which contains cells with bizarre nuclei, (see ▶ Chap. 10, "Mesenchymal Tumors of the Uterus").

Adenomyoma and Papillary Adenofibroma

These neoplasms are rare and are composed of an admixture of fibroconnective tissue and smooth muscle elements intermingling with glands lined by a predominately endocervical type epithelium. The tumors typically measure 1.3–8.0 cm in diameter and usually present as asymptomatic cervical polyps (Gilks et al. 1996). The epithelial component is typically composed of irregular, large glands that may be accompanied by smaller glands in a lobular arrangement. These tumors can be distinguished from endocervical adenocarcinomas by the lack of invasion of the stromal component by the epithelial component, lack of nuclear atypia, and minimal mitotic activity. Adenomyomas can persist or recur, but there are no reported instances of extracervical spread or metastasis (Gilks et al. 1996).

Papillary adenofibromas are rare benign neoplasm with histological characteristics similar to the ovarian adenofibroma. Only several cases have been reported in the literature. They consist of an admixture of fibroconnective tissue and glands lined by either endocervical-type epithelium or a tubal-type epithelium. The fibroconnective tissue usually forms papillary projections (Fig. 49) (Abell 1971; Fratini and Cavaliere 1996).

Miscellaneous Tumors

Hemangiomas are rarely found in the cervix. They may be of capillary or cavernous type (Gudson 1965; Busca and Parra-Herran 2016). A single instance of cervical lymphangioma has been reported and several cases of lipoma of the cervix are on record (Stout 1943). Neoplasms of neurogenic derivation arising in the cervix are extremely rare and include neurofibroma and ganglioneuroma. Benign blue nevi of the

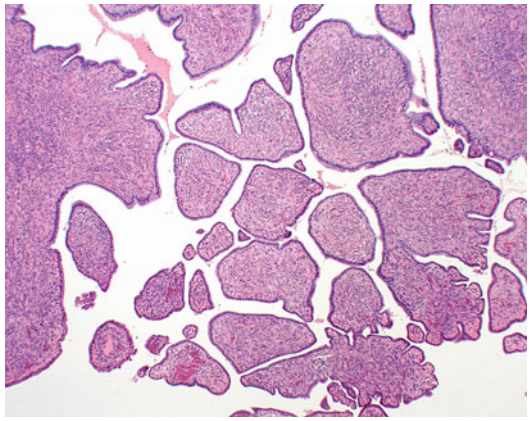

Fig. 49 Papillary adenofibroma of the endocervix. Fibroepithelial papillae project from the cervix. The papillae are covered with endocervical type epithelium

endocervix, indistinguishable from those arising in the dermis, are seen occasionally (Patel and Bhagavan 1985). They are composed of melanin-containing fusiform cells with dendritic cytoplasmic processes, located in the stroma of the endocervix. Cervical melanosis is an uncommon finding characterized by hyperpigmentation of the cervical basal epithelium. It is reported to occur either with or without accompanying basal melanocytes (Yilmaz et al. 1999).

Cysts

Nabothian Cyst

Nabothian cysts are the most common type of cyst of the cervix and develop within the transformation zone secondary to squamous metaplasia covering over and obstructing endocervical glands. Grossly, these lesions appear as yellow white cysts that are frequently multiple and can measure up to 1.5 cm in diameter. Microscopically, they are lined by a somewhat flattened, single layer of mucin-producing endocervical epithelium (Fig. 50). In some cases, squamous metaplasia of the lining epithelium occurs. The lining epithelium is almost always at least focally positive with mucicarimine stains allowing these lesions to be distinguished from

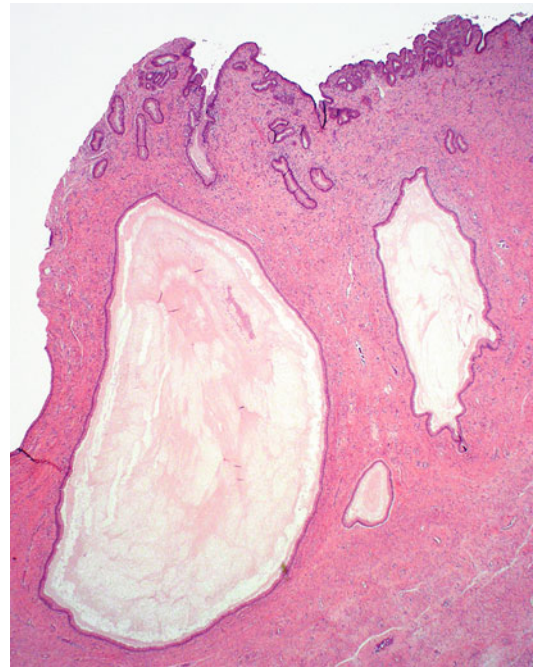

Fig. 50 Nabothian cysts. Nabothian cysts are lined by a flattened layer of mucin-producing epithelium

traumatic inclusion cysts and mesonephric duct cysts. Although nabothian cysts are usually confined to the superficial portion of the cervix, they may extend through the wall of the cervix (Clement and Young 1989).

Tunnel Clusters

Endocervical tunnel clusters are benign collections of endocervical glands that are usually located close to the surface epithelium of the cervix. Tunnel clusters are quite common and become more prevalent with increasing age. In Fluhmann's original description of this condition, they were detected in 8% of all adult women and 13% of the postmenopausal women (Fluhmann 1961b). They appear to be more common in pregnant women. These lesions are asymptomatic and are detected as incidental findings in either hysterectomy specimens or cone biopsies obtained for unrelated reasons (Segal and Hart 1990).

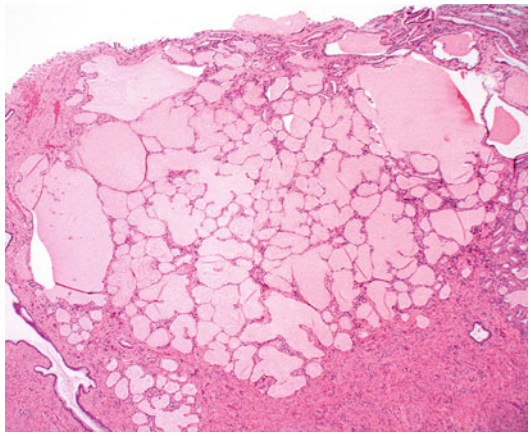

Fig. 51 Endocervical tunnel cluster. Closely packed cystically dilated glands lined by a flattened epithelium. The condition is well-demarcated and does not extend beyond the depth of the normal endocervical glands

Two types of tunnel clusters were originally described. One type represents a cluster of closely packed glands that are noncystic and are lined by tall columnar epithelium. The other type is grossly cystic and lined by a cuboidal or flattened epithelium (Fig. 51). These collections of glands have a clustered appearance with a rounded margin and do not invade into the deep cervical stroma. The importance of tunnel clusters is that they are occasionally misinterpreted as minimal deviation adenocarcinomas of the cervix (Segal and Hart 1990; Jones and Young 1996). However, tunnel clusters do not have nuclear atypia and mitotic activity and most importantly do not invade into the deep cervical stroma.

Inclusion Cyst

Traumatic inclusion cysts are a form of epidermal inclusion cysts that commonly occur in the vagina at sites of surgical repair of episiotomies or vaginal intrapartum lacerations. They are thought to develop from viable fragments of epithelium which become entrapped within the stroma at the time of obstetrical trauma or subsequent surgical repair. Inclusion cysts are uncommonly found on the cervix. Grossly, they present as unilocular cystic structures measuring 1–2 cm in diameter beneath the native portio epithelium (Nikolaou et al. 2014). Microscopically, traumatic inclusion cysts are lined by a stratified squamous epithelium similar to that of the vaginal mucosa but usually somewhat thinner. The epithelium shows normal maturation with the basal cells oriented away from the cyst cavity that is filled with desquamated epithelial cells. The cyst contents are identical to those of epidermal inclusion cysts at other sites and are thick, white and cheesy.

Tumor-Like Lesions

Decidual Pseudopolyp

The gross appearance of the pseudodecidual change that can occur during pregnancy depends on the site. If the change occurs on the exocervix, it frequently presents as a raised plaque or pseudopolyp that can be mistaken for invasive carcinoma both colposcopically and microscopically. During gestation, cervical polyps may also contain focal stromal pseudodecidual changes and rarely massive decidualization of endocervical stroma occurs producing a polypoid protrusion from the endocervix. Clinically, decidualized polyps need to be differentiated from extruded fragments of decidua that may indicate an impeding miscarriage. Distinction is made by identifying a stalk for the decidualized polyp, whereas expulsed fragments of decidua lack a stalk. Areas of pseudodecidualization are microscopically differentiated from invasive nonkeratinizing squamous cell carcinoma by the lack of significant nuclear atypia, as well as lack of mitotic figures, a coexisting SIL and continuity with the surface epithelium. In difficult cases, immunohistochemistry using antibodies against cytokeratin proteins can be used to differentiate cytokeratin negative decidual reactions from cytokeratin positive nonkeratinizing squamous cell carcinoma.

Mullerian Papilloma

Rare instances of a benign, papillary growth of the cervix that occur primarily in children have been described (Seltzer et al. 1979; Lane et al. 2005;

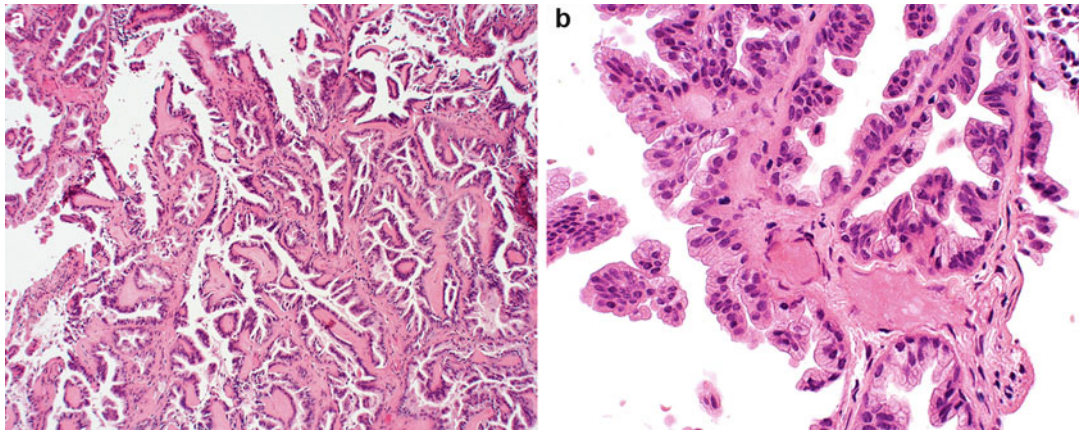

Fig. 52 Mullerian papilloma. (**a**) Papillary projections are (**b**) covered with a flattened cuboidal epithelium

Hollowell et al. 2007). They are composed of complex papillary projections lined by flat cuboidal epithelium with cores of loose fibrovascular tissue (Fig. 52a, b). Cytologic atypia and mitoses are absent. In the past, the lesions were thought to be of mesonephric duct origin, although they have not been encountered in association with mesonephric remnants. Although the histogenesis of these lesions remains uncertain, recent studies favor a Mullerian origin.

Postoperative Spindle Cell Nodule and Inflammatory Pseudotumor

Postoperative spindle cell nodules of the cervix are clinically and histologically identical to their more common counterparts of the vulva and vagina (Kay and Schneider 1985; Proppe et al. 1984). These lesions may develop after either a cervical biopsy or some other form of trauma. They resemble nodular fasciitis and are composed of actively proliferative spindle cells with oval nuclei arranged in interlacing bundles (see Fig. 19 in ▶ Chap. 3, "Diseases of the Vagina"). The cells may vary slightly in size and mitotic figures are often present. A characteristic feature is the presence of neutrophils and erythrocytes in the lesion, giving it the appearance of granulation tissue.

Inflammatory pseudotumor refers to a closely related lesion to postoperative spindle cell nodule that occurs in the absence of a known history of trauma (Abenoza et al. 1994). Inflammatory pseudotumor is a proliferative process of unknown etiology with a polymorphic appearance. The lesions contain two cellular components; a fibrohistiocytic component consisting of fibroblasts, myofibroblasts, and histiocytes; and a polymorphous inflammatory component consisting of lymphocytes and plasma cells. The lesion can be differentiated from other neoplastic processes by the lack of atypia and mitoses and the presence of a polymorphous inflammatory infiltrate.

Lymphoma-Like Lesions

Lymphoma-like lesions (pseudolymphomas) are marked inflammatory lesions of the cervix, extensive enough to cause confusion with a lymphoproliferative lesion (Young et al. 1985). Lymphoma-like lesions are composed of a superficial band of large lymphoid cells admixed with mature lymphocytes and plasma cells. The lymphoid infiltrates commonly include macrophages and germinal centers which help to distinguish them from lymphomas (Fig. 32). Another feature, which helps to distinguish lymphoma-like lesions from lymphomas, is the superficial localization of the infiltrate. Lymphoma-like lesions rarely infiltrate deeper than 3 mm from the surface epithelium whereas lymphomas of the cervix usually extend beyond the depth of the endocervical glands (see ▶ Chap. 6, "Carcinoma and Other Tumors of the Cervix").

Heterologous Tissue

Glia

There are 15 recorded cases of neuroglial tissue in the cervix or the endometrium (see ▶ Chap. 7, "Benign Diseases of the Endometrium") (Slavutin 1979). Although the term glioma is used for this condition, the high degree of differentiation of the glial tissue, the absence of mitoses, and the absence of recurrence are against the lesion being neoplastic. The lesion should not be confused with a pure heterologous sarcoma or a teratoma. The neural tissue is believed to represent either implantation of fetal cerebral glia at the time of instrumentation of the gravid uterus or heterotopic maldevelopment during embryogenesis. When the cervix is involved, the lesion usually appears as a polyp that bleeds readily.

Ectodermal Structures

Among the pathologic curiosities of the cervix are cases of true epidermidization of the cervical mucosa. In these rare instances, sebaceous glands, hair, sweat glands and occasionally mantle structure are found. These ectodermal structures are usually either attached to the basal layer of the squamous epithelium or are isolated in the cervical stroma. The squamous epithelium overlying the ectodermal structures often shows hyperkeratosis (Brady and McCluggage 2013). The presence of these ectodermal structures, which are normally appendages of the epidermis, on a mucous membrane of mesodermal derivation is difficult to explain. One theory is that the ectodermal structures represent misplaced embryonal tissue. It is conceivable, however, that stratified squamous epithelium under certain circumstances, such as long-standing chronic inflammation can form ectodermal structures by a metaplastic process (Brady and McCluggage 2013; Kazakov et al. 2009).

Cartilage

Four cases of heterotopic mature cartilage in the cervix are on record (Roth and Taylor 1966). The finding of these structures alone has no clinical significance. They should not be confused with a malignant mesodermal mixed tumor.

Prostatic Tissue

There have been a number of reports of ectopic prostatic tissue being identified in the cervix (McCluggage et al. 2006; Kelly et al. 2011; Nucci et al. 2000). These foci are usually identified as incidental lesions in women undergoing a hysterectomy or an excision procedure for treatment of a cervical cancer precursor. However, if the ectopic prostatic tissue is abundant and hyperplastic appearing, it can form a discrete tumor-like mass (Nucci et al. 2000). The lesions are usually located on the ectocervix beneath the surface epithelium. Histologically, they appear as well-demarcated nests of epithelial cells that usually contain both squamous and glandular or tubular elements (Fig. 53a). The extent of squamous and glandular elements varies considerably with some lesions consisting almost entirely of squamous elements whereas others consist predominantly of glands or tubules. The glandular or tubular elements have intracytoplasmic mucin and the glandular elements can have a papillary or cribiform architecture but lacks mitotic activity and nuclear atypia. Sometimes the glandular component can have two cell layers with an outer basal cell layer consisting of small flattened cells and an inner columnar cell layer with abundant vacuolated cytoplasm.

By immunohistochemistry, the squamous component is usually diffusely positive for GATA3 whereas the glandular component is negative (Fig. 53b). The glandular component frequently stains positively for prostatic acid phosphatase (PrAP) and prostate-specific antigen (PSA) (Kelly et al. 2011). Recently, it has been reported that the glandular component stains with NKX3 (Fig. 53c) which is an androgen-regulated, prostate-specific transcription factor that plays a role in prostate development and tumor suppression (Roma 2016).

The origin of ectopic prostatic tissue in the cervix is unclear. Although it may represent a form of metaplasia, given its usual location on the ectocervix and the fact that histologically it closely resembles tubulosquamous polyps of the vagina, it more likely represents a developmental

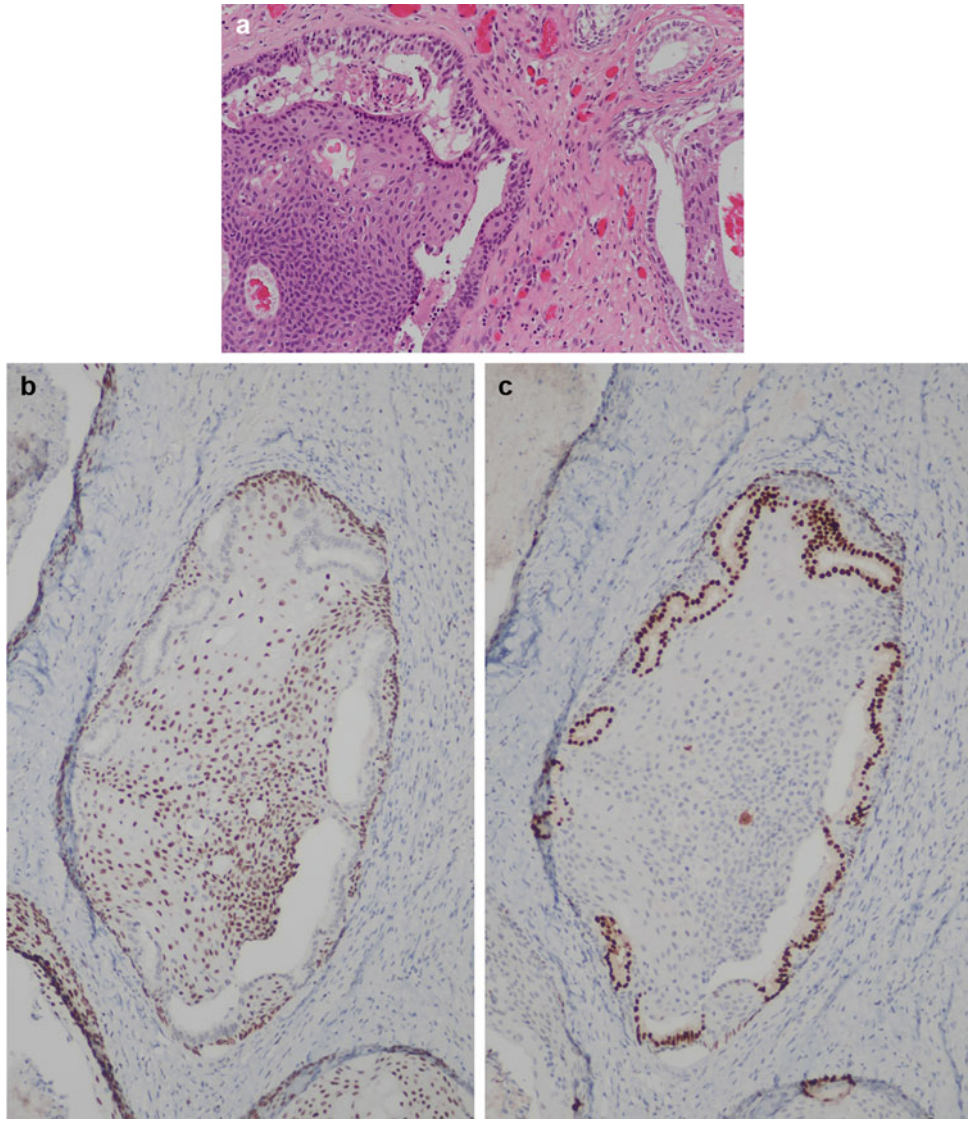

Fig. 53 Tubulosquamous polyp with ectopic prostate. (**a**) There is a mixture of squamous and glandular or tubular elements. (**b**) The squamous elements stain positively for GATA3. (**c**) The glandular elements stain positively for NKX 3

anomaly in which the periurethral Skene's glands are misplaced during embryonic development (Kelly et al. 2011; Nucci et al. 2000; Roma 2016). This lesion is sometimes confused with adenoid basal tumor/epithelioma. p16 is useful for distinguishing these lesions, as ectopic prostatic tissue is negative or focally positive for p16 whereas adenoid basal tumors are diffusely positive due to the presence of high-risk HPV.

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