Benign Lesions and Physiologic Changes in the Cervix

3

Lynn N. Hoang

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This chapter describes the various metaplastic, inflammatory, infectious and reactive conditions which can affect the uterine cervix.

3.1 Squamous Metaplasia

3.1.1 Definition

Squamous metaplasia is a normal physiological process in which endocervical cells are replaced by squamous cells in the transformation zone.

3.1.2 Synonyms

None.

3.1.3 Etiology

Squamous metaplasia is a normal process in post-pubertal women; cervical ectropion, a colposcopic finding composed of glandular epithelium in the ectocervix, is followed by replacement of the glandular epithelium with squamous epithelium due to the acidic milieu of the vagina. Incomplete replacement can be seen as immature squamous metaplasia or incomplete persistence of the endocervical glands.

3.1.4 Macroscopy

On colposcopy, squamous metaplasia in the transformation zone is usually sharply demarcated. It has a pale pink or white-pink color. The immature squamous cells do not contain glycogen and thus will not stain with Lugol's iodine solution. Application of acetic acid may cause immature squamous epithelium to turn mildly white, which can be a source of confusion for the beginner gynecologist.

3.1.5 Microscopy

Squamous metaplasia is composed of a spectrum of appearances. In typical squamous metaplasia, non-keratinizing squamous cells have approximately a 1:1 nuclear-to-cytoplasmic (N:C) ratio, higher than that of normal squamous epithelium (Fig. 3.1). So-called "immature squamous metaplasia" contains similar-appearing cells with even higher nuclear-to-cytoplasmic ratios. Cells appear crowded, but lack disorganization. The superficial layer of the squamous mucosa lacks cytoplasmic maturation. Nuclei have uniform chromatin and smooth nuclear contours. Rare mitoses can be seen, but no atypical mitotic forms. Mucin droplets or retained endocervical cells can sometimes be seen in the superficial layers. Architecture can be lobular or nested, particularly when extending into the endocervical glands. Papillary architecture and koilocytic atypia should not be seen. The cells are positive for p63, CK17 (a marker of reserve cells that give rise to squamous metaplasia, seen in a bottom-heavy pattern), and CK7 (top-heavy pattern). It is negative for p16 (patchy or absent staining), and the Ki-67 proliferation index is low [1–5].

3.1.6 Differential Diagnosis

- Squamous metaplasia is most often mistaken for a *high-grade squamous intraepithelial lesion* (HSIL). HSIL will show epithelial disorganization, nuclear atypia,

Diagnostic Highlights

- Monotonous crowded squamous cells with higher N:C ratio and lack of cytoplasmic maturation in upper layers, occurring in post-pubertal women
- Cells are still organized and nuclei are not atypical
- Retained endocervical cells can sometimes be seen in the superficial layers

hyperchromasia, and suprabasal mitoses. HSIL also will show "block-like" positivity for p16 and negativity for CK17 [1, 4, 5]. A subset of papillary immature squamous metaplasia harbors low-risk human papillomavirus (HPV), and this finding should prompt a search for HPV-related histologic features such as koilocytes, binucleation, or nucleomegaly [6].

- Florid squamous metaplasia in endocervical glands or endocervical polyps can mimic *well-differentiated squamous cell carcinoma*. The nests in squamous metaplasia will have smooth contours and lack cytologic atypia (see Fig. 3.1e).
- Detached fragments of squamous metaplasia also can be found in association with *endometrioid adenocarcinoma of endometrium* (see Fig. 3.1f). Careful search for atypia and mitoses, as well as prototypical areas of endometrioid carcinoma, should be undertaken.

3.1.7 Prognosis

Benign.

Case A 39-year-old woman has a hysterectomy for known uterine fibroids (Fig. 3.1).

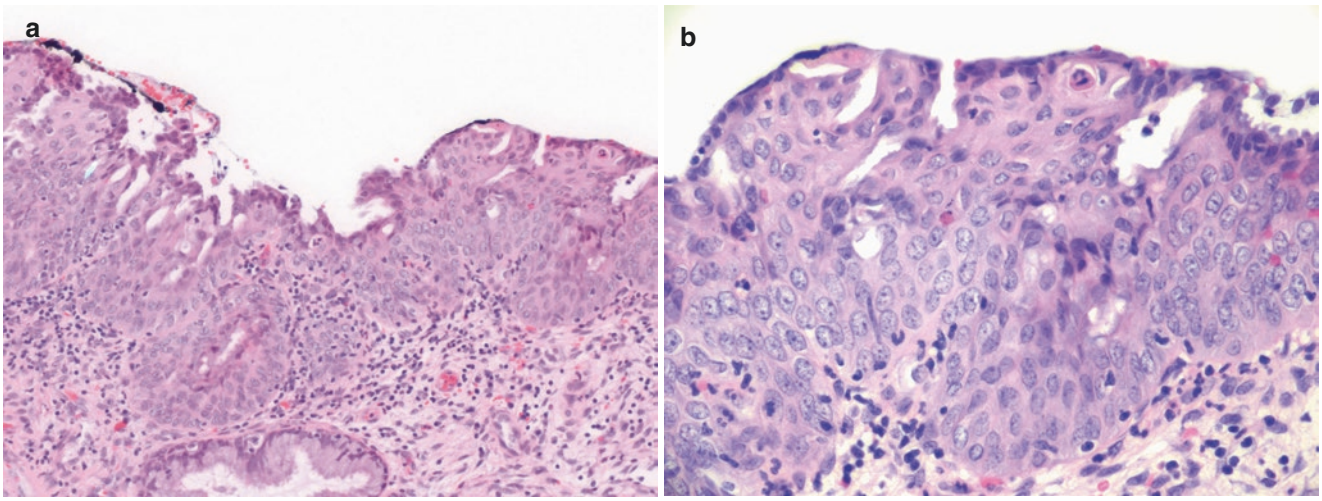

Fig. 3.1 Squamous metaplasia. *Case history:* A 39-year-old woman undergoes a hysterectomy for known uterine fibroids. Examination of the uterine cervix shows a proliferation of basaloid cells within the squamocolumnar junction of the cervix. (**a**) The cells have a high nuclear-to-cytoplasmic (N:C) ratio and show focal extension into the underlying endocervical glands. (**b**) The cells are crowded but lack disorganization, hyperchromasia, and suprabasilar mitoses. The nuclei are round, with smooth nuclear contours and open chromatin. Care should be taken to not mistake this for a high-grade squamous intraepithelial lesion (HSIL). (**c**) Retained endocervical glands can be seen in the superficial layer of the mucosa. (**d**) p16 shows patchy staining. (**e**) Squamous metaplasia involving an endocervical polyp appears florid. The smooth contours of each squamous nest and the lack of atypia help to rule out an invasive squamous cell carcinoma. (**f**) For comparison, these are fragments of squamous metaplasia in a different patient, found in association with endometrioid adenocarcinoma

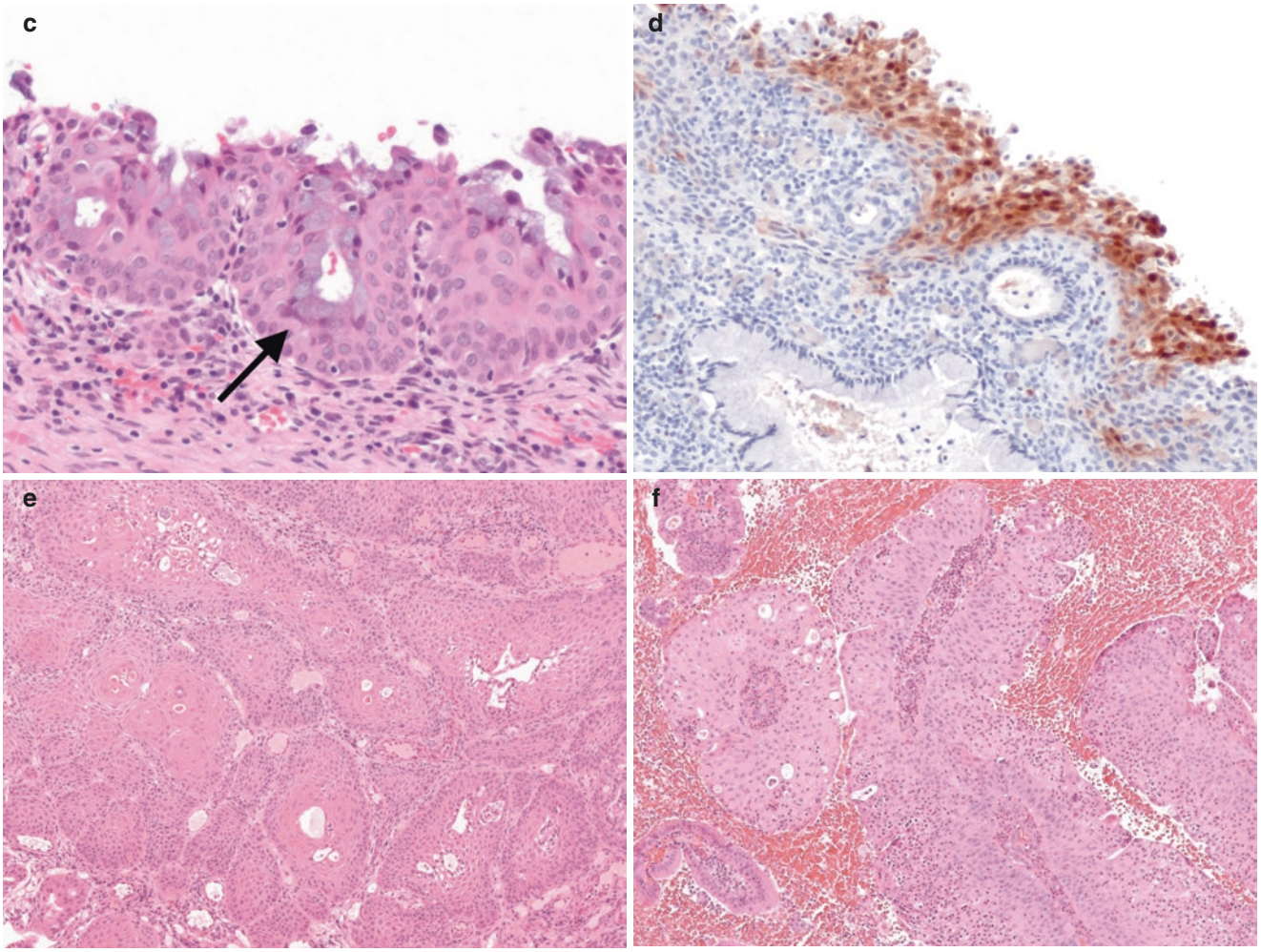

Fig. 3.1 (continued)

3.2 Transitional Metaplasia

3.2.1 Definition

The squamous cells of the ectocervix are replaced with transitional-like epithelium. The term *transitional* is a misnomer. The squamous ectocervical epithelium is atrophic and appears transitional-like, but it does not represent true transitional/urothelial epithelium.

3.2.2 Etiology

Transitional metaplasia is thought be related to hypoestrogenism. It is usually encountered in postmenopausal women and in genetic females who receive androgen therapy for gender reassignment [7].

3.2.3 Macroscopy

Transitional metaplasia is an incidental finding, which is not macroscopically visible.

3.2.4 Microscopy

The squamous ectocervical epithelium comprises multiple layers of cells with an increased N:C ratio (Fig. 3.2). The nuclei are uniform, oval, and can have longitudinal nuclear grooves. The nuclei are vertically oriented in the deeper layers and horizontally oriented in the superficial layers, with a vague, streaming-like appearance [8]. Perinuclear halos may be present. On Pap smears, transitional metaplasia can result in atypical squamous cells, cannot rule out high-grade lesion (ASC-H) [9]. p63 is positive, p16 and CK20 are negative [10].

Diagnostic Highlights

- Squamous cells with increased N:C ratio, lacking mitotic activity and hyperchromasia, occurring in post-menopausal women
- Cells are uniform, oval and can have longitudinal nuclear grooves and a streaming-like appearance

3.2.5 Differential Diagnosis

- The elevated N:C ratio often causes confusion with *HSIL*, but in transitional metaplasia the cells have bland nuclei, lack mitotic activity, and are p16 negative (*see* Fig. 3.2d) [7].

3.2.6 Prognosis

Benign.

Case A 61-year-old woman has a hysterectomy for abnormal uterine bleeding. The ectocervix shows thin mucosa with basaloid cells (Fig. 3.2).

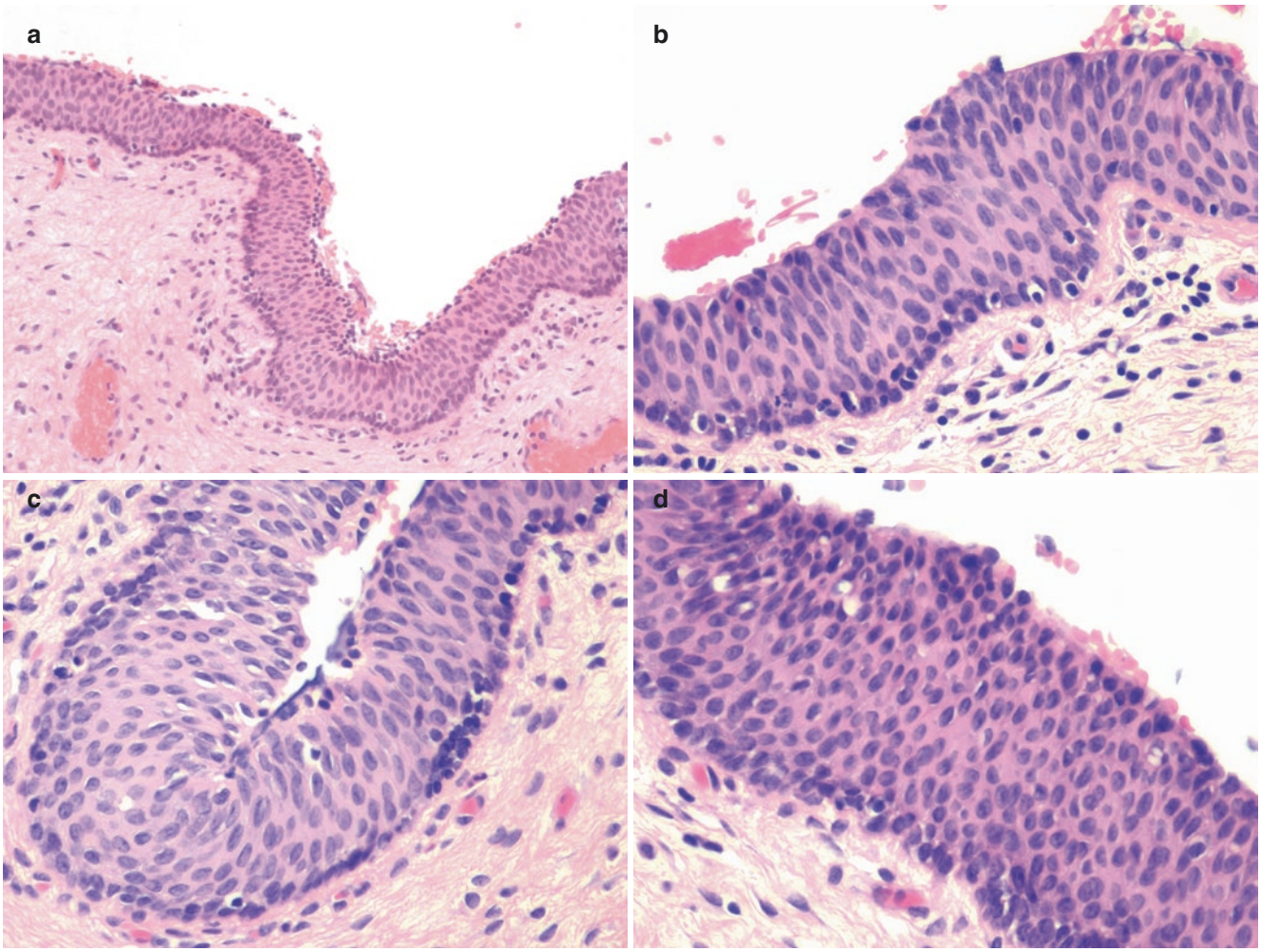

Fig. 3.2 Transitional metaplasia. *Case history:* A 61-year-old woman has a hysterectomy for abnormal uterine bleeding. The ectocervix shows thin mucosa with basaloid cells. (**a**) The ectocervical mucosa is thin and composed of basaloid cells with scant cytoplasm. (**b**) The cells have a high N:C ratio and ovoid nuclei, which are arranged perpendicular to the basement membrane. (**c**) The cells have a streaming appearance. (**d**) In other areas, the mucosa is not as thin. The cells appear crowded but organized. They lack hyperchromasia, atypia, and mitotic activity. This appearance can mimic that of HSIL

3.3 Tubal and Tubo-Endometrioid Metaplasia

3.3.1 Definition

The endocervical epithelium is replaced with tubal or mixed tubal-endometrioid epithelium.

Diagnostic Highlights

- Presence of tubal (ciliated and secretory cells)
- The glands, when multiple, may show some variation in size and are not always evenly spaced. Periglandular stromal hypercellularity or edema is common.
- p16 is negative (absent or patchy) and Ki67 proliferation index is low

3.3.2 Etiology

Tubal and tubo-endometrioid metaplasia is a common finding, seen in up to two-thirds of hysterectomy specimens. It is thought to be a regenerative process related to prior procedures (biopsy, cone, LEEP) (Fig. 3.3) [11].

3.3.3 Macroscopy

These are incidental findings, which are not macroscopically visible.

3.3.4 Microscopy

Endocervical surface or glandular epithelium is replaced by a single layer of admixed ciliated cells and non-ciliated cells (secretory cells, peg cells) in varying proportions. The non-ciliated (secretory) cells may have apical snouts. In tubo-endometrioid metaplasia, the ciliated cells are fewer in number. The glands, when multiple, may show some variation in size and are not always evenly spaced. Mild periglandular stromal hypercellularity or edema is common [12]. Immunohistochemical staining is negative for p16 (absent or patchy "tiger-stripe" staining) and positive for BCL2 (see Fig. 3.3g, h) and PAX2. The Ki-67 proliferation index is low (typically <10%) [13].

3.3.5 Differential Diagnosis

- Tubal and tubo-endometrioid metaplasia can appear mildly hyperchromatic when compared with the background endocervical mucinous epithelium and may be confused with *adenocarcinoma in situ (AIS)*. In contrast to AIS, there will be an absence of apical mitoses, absence of apoptotic debris, and patchy p16 staining. The mild architectural irregularity and crowding should also not be confused with an infiltrative malignant process.
- p16 in tubal and tubo-endometrioid metaplasia can exhibit a patchy ("tiger-stripe" or "piano-key") pattern. This pattern should not be considered positive and should not be confused with the diffuse block-like p16 staining seen in AIS (see Fig. 3.3g).

3.3.6 Prognosis

Benign.

Case A 42-year-old woman had a prior loop electrosurgical excision procedure, which showed adenocarcinoma in situ. She then has a hysterectomy which shows an irregular proliferation of glands (Fig. 3.3).

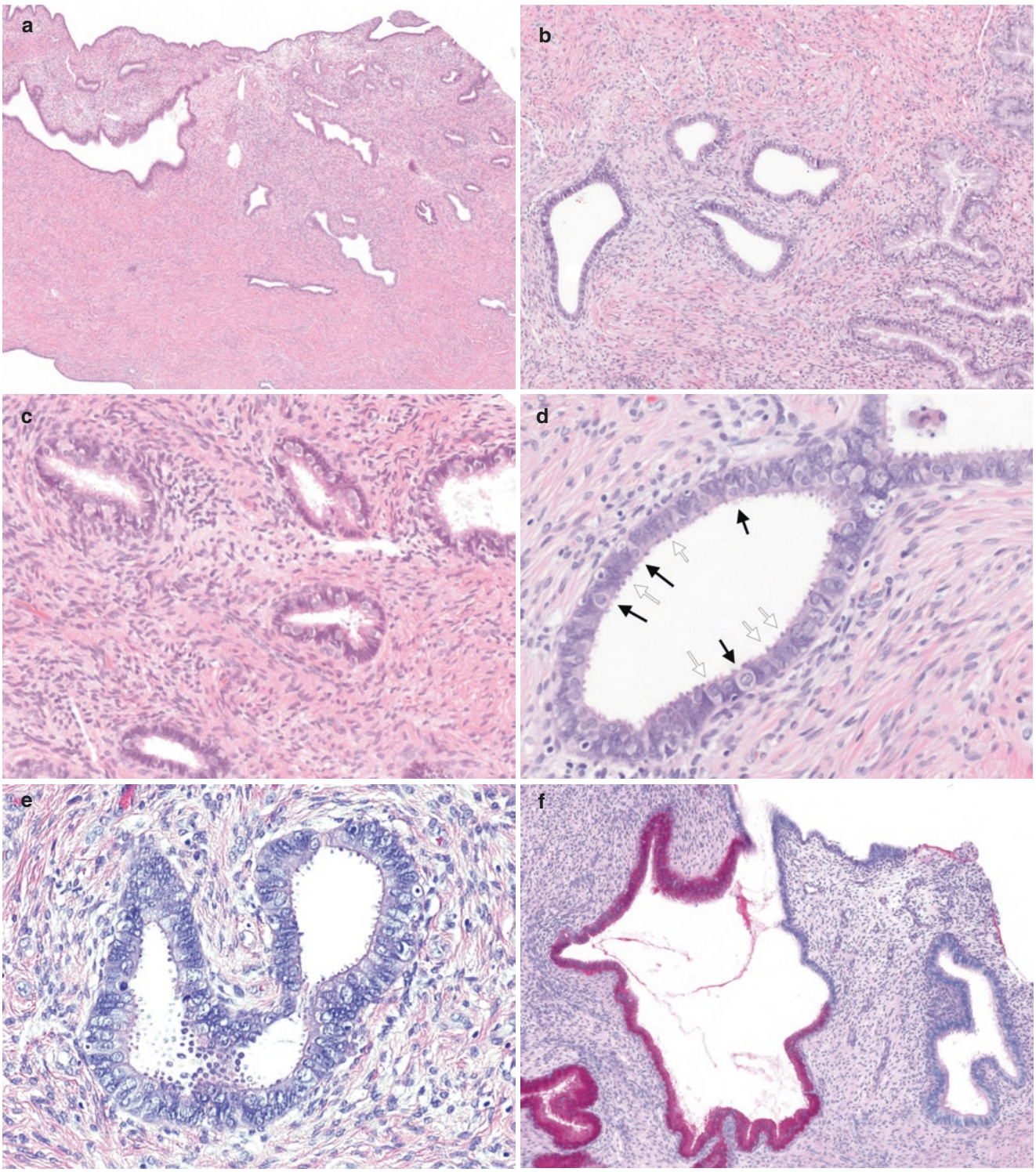

Fig. 3.3 Tubal Metaplasia. *Case history:* A 42-year-old woman had a prior loop electrosurgical excision procedure (LEEP), which showed adenocarcinoma in situ (AIS). The subsequent hysterectomy (shown here) contains an irregular proliferation of glands in the cervix. A glance at the glands raises the possibility of residual AIS, but further examination shows that they represent tubal metaplasia. (**a**) The glands have irregular architecture and shapes, but do not appear crowded. (**b**) The glands (*left*) appear hyperchromatic on a low-power view; the adjacent endocervical glands (*right*) contain ample mucinous cytoplasm. (**c**) On higher power, the glands contain two types of cells, one with pale, eosinophilic cytoplasm and the other with darker, amphophilic cytoplasm. (**d**) On high power, the ciliated cells have pale, eosinophilic cytoplasm and apical cilia (*black arrows*). The non-ciliated cells have amphophilic cytoplasm and apical snouts (*white arrows*). (**e**) Focally, the cells appear atypical. The nuclei are mildly enlarged, and scattered mitotic figures are seen. (**f**) PAS stains show that the glands (*right*) do not contain mucin, in comparison to the normal endocervical mucinous cells (*left*). (**g**) p16 shows staining in a patchy, tiger-stripe pattern, which is considered negative. Diffuse block-like staining and high-risk HPV in situ hybridization would be seen in AIS. (**h**) BCL2 (a tumor suppressor) is positive (retained). Loss of BCL2 and PAX2 would be seen in AIS

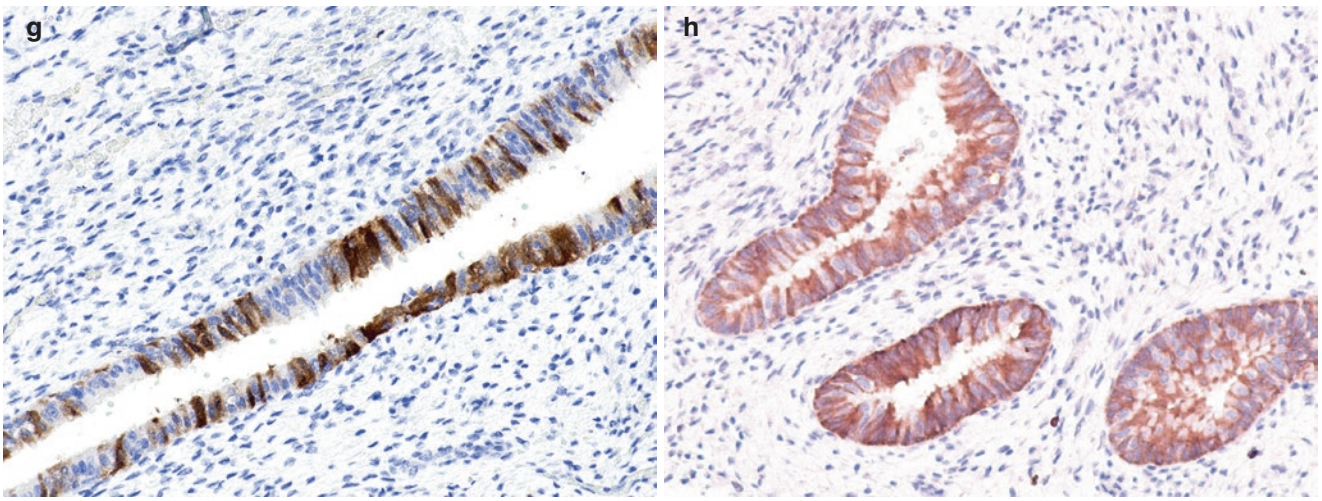

Fig. 3.3 (continued)

3.4 Endometriosis

3.4.1 Definition

Endometrial glands and stroma involving cervical mucosa or stroma.

3.4.2 Etiology

Endometriosis usually occurs in sites of prior cervical trauma including prior surgery (biopsy, conization) and childbirth, suggesting preferential implantation of endometrial tissue on traumatized cervical tissue, or regeneration-related metaplasia. Deep endometriosis is usually an extension of cul-de-sac involvement from pelvic endometriosis.

3.4.3 Macroscopy

Endometriosis can cause thickened, hemorrhagic, or granular mucosa (Fig. 3.4).

3.4.4 Microscopy

The bland endometrial glands are well-spaced, round to oval, and can have secretory or proliferative changes (including mitotic activity). The endometrial glands are usually accompanied by endometrial stromal cells. The stromal cells have scant cytoplasm and bland nuclear features, as well as a background of small, delicate arterioles. More abundant stromal cell cytoplasm is found when decidualized or pseudo-decidualized. Hemorrhage, edema, hemosiderin-laden macrophages, and inflammation may be seen.

Diagnostic Highlights

- Presence of endometrial glands and stroma in the cervix
- Often seen within a prior surgical site (i.e. LEEP site)

3.4.5 Differential Diagnosis

- The mitotic activity and reactive atypia in endometriosis can be confused with adenocarcinoma in situ (AIS) [14]. In endometriosis, p16 is negative and BCL2 is positive; the opposite pattern applies in AIS.
- Cervical endometriosis can consist exclusively of endometrial stroma ("gland-poor" or "stroma-only" endometriosis). This appearance, in combination with the "pseudoinfiltrative" pattern of endometriosis, may be confused with a low-grade endometrial stromal sarcoma (see Fig. 3.4e, f). Search for more typical areas of endometriosis will be informative.
- Ectopic decidua can occur in up to one third of cervical biopsies in pregnancy but usually disappears by 8 weeks postpartum. It appears finely granular and tan-white on speculum examination. When biopsied, the stromal cells are plump and eosinophilic (decidualized) (see Fig. 3.4c).

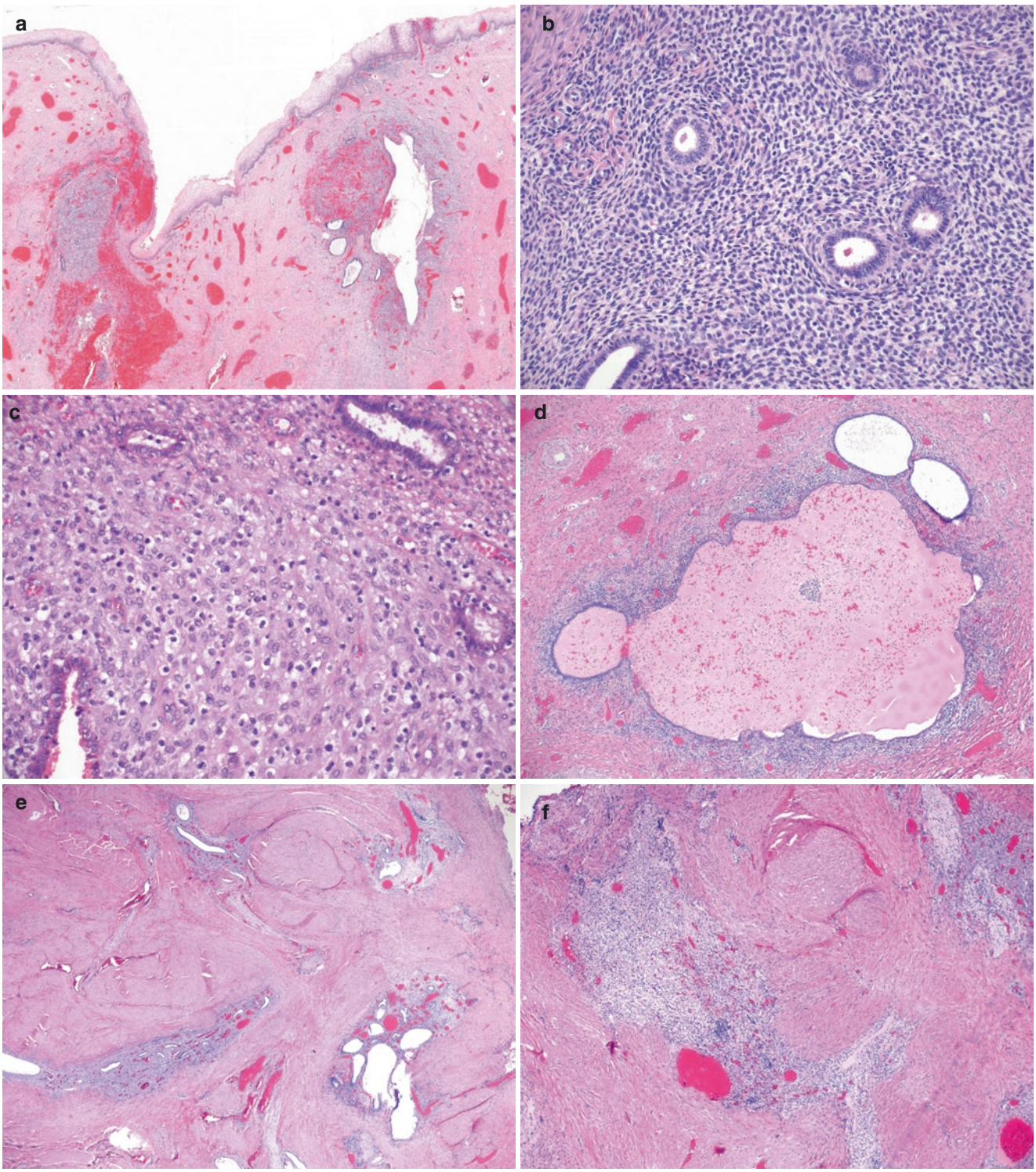

Fig. 3.4 Endometriosis. *Case history:* A 35-year-old woman has a hysterectomy for dysmenorrhea and dyschezia. (**a**) The cervix is hemorrhagic, and areas contain endometrial glands and stroma. (**b**) The endometrial glands are cuboidal to columnar, with scattered mitoses. The endometrial stromal cells consist of small blue cells with scant cytoplasm. (**c**) For comparison, this cervical endometriosis is from a different patient, who was taking oral progestins. The cytoplasm of these stromal cells is plump and eosinophilic (pseudo-decidualized). (**d**) The endometrial glands have become cystic and contain hemosiderin-laden macrophages in the stroma and lumen. (**e**) This patient's cervical endometriosis is an extension of pelvic endometriosis, extending from the cul-de-sac. The endometrial glands and stromal cells can have a pseudo-infiltrative appearance. (**f**) Areas of endometriosis can be gland-poor and mimic the appearance of a low-grade endometrial stromal sarcoma. (**g**) CD10 is positive in the endometrial stromal cells surrounding the endometrial glands. The stroma of the cervix is negative or weakly positive. (**h**) For comparison, this is a focus of endometriosis in a prior LEEP site from another patient. The foci are surrounded by hemorrhage, inflammation, and vascular ectasia

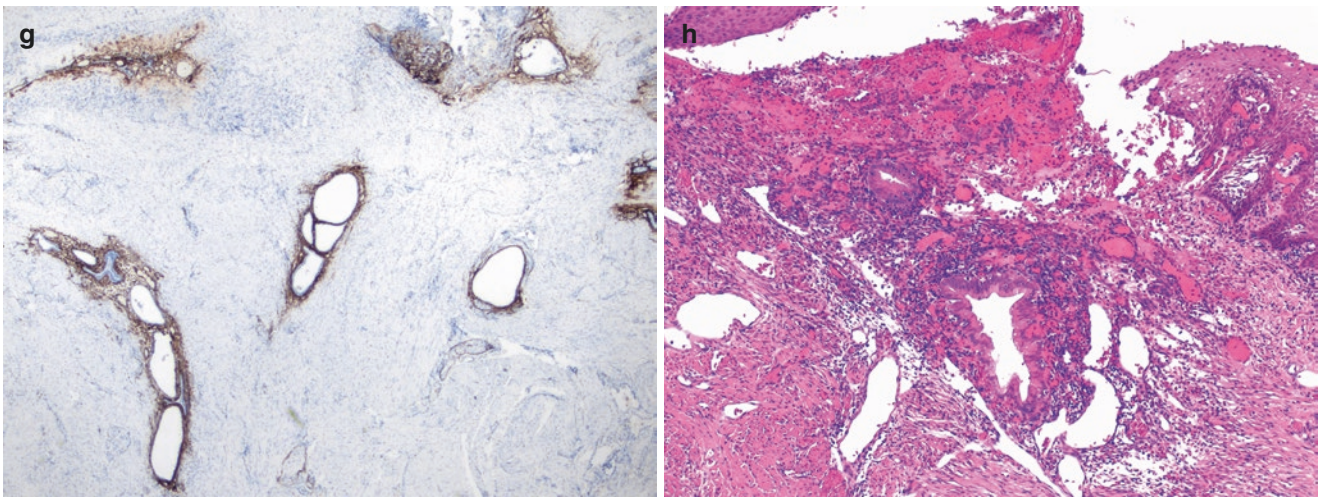

Fig. 3.4 (continued)

3.4.6 Prognosis

Benign.

Case A 35-year-old woman has a hysterectomy for dysmenorrhea and dyschezia (Fig. 3.4).

3.5 Other Metaplasias

3.5.1 Definition

The cervical mucosa can be replaced by intestinal, gastric (pyloric), and oxyphilic epithelium.

3.5.2 Etiology

The etiology is unknown. A small subset may be due to a reparative process or a genetic syndrome (Peutz-Jeghers syndrome).

3.5.3 Microscopy

Intestinal metaplasia consists of goblet cells and, occasionally, argentaffin or neuroendocrine cells [15]. Gastric (pyloric) metaplasia is much more histologically subtle, characterized by high columnar cells containing ample pale or eosinophilic cytoplasm, basally located nuclei and well-defined intercellular membranes. It is positive for HIK1083 and MUC6 [16]. Oxyphilic metaplasia consists of large cells with dense eosinophilic cytoplasm, variably vacuolated cytoplasm, hyperchromatic nuclei, and multinucleation. It is usually very focal, involving only a single gland or a few glands [17].

Diagnostic Highlights

- Intestinal metaplasia consists of glands with goblet cells or argentaffin cells, but usually retain a Mullerian immunophenotype.
- Gastric (pyloric) metaplasia contains bland mucinous cells with ample eosinophilic cytoplasm and basal nuclei, akin to the foveolar mucinous cells seen in the stomach. Goblet cells may be present.

3.5.4 Differential Diagnosis

- Intestinal metaplasia can be found in isolation, but this is very rare. More commonly, intestinal metaplasia is associated with *AIS and squamous intraepithelial lesion* [18, 19]. Similarly, the finding of pyloric metaplasia, with or without intestinal metaplasia, should prompt a rigorous search for *lobular endocervical glandular hyperplasia, minimal deviation adenocarcinoma, and gastric-type adenocarcinoma.*

3.5.5 Prognosis

Benign.

3.6 Ectopic Tissues

3.6.1 Definition

Various ectopic tissue can be found within the cervix.

3.6.2 Etiology

Some tissues may represent a developmental anomaly, a reparative process, or a variant of normal anatomy, but in most cases, the etiology is unknown.

3.6.3 Macroscopy

Some ectopic tissue may present as a mass lesion, although most are incidental findings.

3.6.4 Microscopy

Ectopic prostate tissue Prostatic glandular tissue comprises basal cells, secretory cells, and in some cases, squamous metaplasia. The cells are positive for prostate-specific antigen (PSA), prostate-specific acid phosphatase (PSAP), NKX3.1 and sometimes androgen receptor (AR) [20, 21]. Squamous elements can be estrogen-receptor (ER) positive [22].

Epidermoid metaplasia This consists of various combinations of sebaceous glands, basaloid cells, hair follicles, excretory ducts, and melanin pigment [23–26].

Ectopic bone Mature trabecular bone (with or without associated bone marrow cells) may occur at the site of a prior loop electrosurgical excision procedure [27–31].

Glial tissue Mature glial tissue consists of fine, eosinophilic, spindled and fibrillary tissue. It is positive for glial fibrillary acid protein (GFAP) and S100. Genotyping has shown it to represent fetal tissue implantation from a prior abnormal pregnancy [32].

Adipose tissue Mature adipose tissue can be found in up to 15% of excision specimens [33].

Diagnostic Highlights

- Various extrinsic tissues within the cervix (prostatic, epidermoid, bone, glial tissue, adipose tissue).

3.6.5 Differential Diagnosis

- The finding of mature osseous or chondroid tissue is likely benign, but pathologists should be cautious in excluding a malignant neoplasm (such as embryonal rhabdomyosarcoma and carcinosarcoma).
- The persence of adipose tissue in an endometrial curettage may signifiy uterine perforation (a critical value in pathology). In some cases, the adipose tissue may be from adipose tissue originating in the uterine cervix.

3.6.6 Prognosis

Benign.

3.7 Microglandular Hyperplasia

3.7.1 Definition

Microglandular hyperplasia (MGH) is a benign complex proliferation of endocervical glands.

3.7.2 Etiology

MGH is driven by estrogen and progesterone (i.e., pregnancy, oral contraceptives). It most often occurs in reproductive-age women, though a small subset may occur in postmenopausal women [34].

3.7.3 Macroscopy

It can sometimes present as a cervical erosion; more commonly, it appears as part of an endocervical polyp.

3.7.4 Microscopy

Proliferation of closely packed endocervical mucinous glands of varying sizes, lined by low columnar, cuboidal, or flattened mucinous cells (Fig. 3.5). Each gland is surrounded by a basal cell layer that is p63 positive, but this layer can be attenuated. Cystic dilatation, subnuclear vacuolization, reserve cell hyperplasia, squamous metaplasia, and complex architecture (cribriform, reticular, trabecular) can be seen. Nuclei are small with inconspicuous nucleoli, and mitoses are rare. Glandular lumens contain inspissated mucin and neutrophils. There is little intervening stroma, but when apparent, there are stromal chronic inflammatory cells. The surface epithelium is usually involved, particularly in endo-

cervical polyps, but extension into the deeper endocervical glands can occur. MGH is positive for estrogen receptor (ER) and progesterone receptor (PR); it is generally negative for p16 [35]. Rarely, florid endocervical glandular hyperplasia can be seen in patients with cystic fibrosis [36].

Diagnostic Highlights

- Proliferation of closely packed endocervical mucinous glands, which can be columnar, cuboidal, or flattened
- Most glands are surrounded by a basal layer
- Reserve cell hyperplasia, squamous metaplasia, and complex architecture (cribriform, reticular, trabecular) can be seen; cells lack nuclear atypia and, for the most part, mitotic activity
- Positive staining for ER and PR with tiger-strip p16 staining, but no block-like staining

3.7.5 Differential Diagnosis

- The diagnosis of MGH in a post-menopausal woman should be made very cautiously, as it is a hormone driven proliferation. The possibility of adenocarcinoma should be carefully considered in this setting.
- Unusual microscopic findings such as complex architectural patterns; edematous, myxoid, or hyalinized stroma; and signet ring or hobnail cells can be found and should not be mistaken for adenocarcinoma [37]. With that being said, the major differential consideration is with *endometrioid adenocarcinoma with mucinous differentiation* (see Fig. 3.5f–h). In so-called "MGH-like" endometrial carcinoma, helpful features include continuity with fragments of prototypical endometrioid carcinoma, stromal foamy macrophages, an older/post-menopausal patient, greater cytologic atypia, and mitotic activity [34, 38, 39]. Vimentin is usually negative in MGH and positive in MGH-like endometrial carcinoma [40].
- When there is stromal hyalinization, MGH can be confused with clear cell carcinoma. Unlike CCC, MGH typically does not form a mass lesion and will not have papillary architecture, diffuse cytoplasmic clearing, cytoplasmic glycogen, or elevated mitotic activity [34].

3.7.6 Prognosis

Benign.

Case An endocervical polyp was removed from a 32-year-old woman (Fig. 3.5).

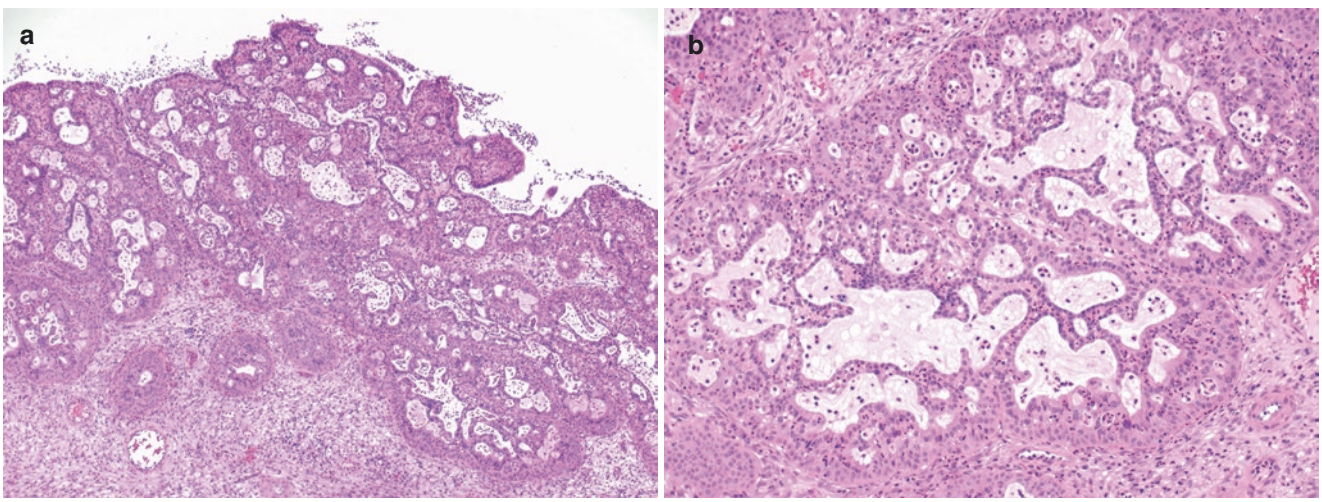

Fig. 3.5 Microglandular hyperplasia. *Case history:* This endocervical polyp was removed from a 32-year-old woman. (**a**) A crowded proliferation of glands, arranged in lobular clusters, involves the surface of this endometrial polyp. (**b**) Each lobular cluster consists of crowded endocervical glands, with vague cribriform architecture. (**c**) Some areas of microglandular hyperplasia have squamous metaplasia undermining the mucinous cells. (**d**) The cytologic features are bland. The nuclei are small, with smooth nuclear contours and open chromatin, and lack mitotic activity. (**e**) p63 helps to highlight the basal (reserve) cells surrounding each lobular cluster of glands. (**f–h**) For comparison, these images show an endometrial endometrioid adenocarcinoma with mucinous differentiation, which can mimic microglandular hyperplasia. The nuclear features can be very bland, but upon thorough examination, mitotic activity and modest nuclear atypia can be seen. Areas of prototypical endometrioid adenocarcinoma (*right*) also can be found

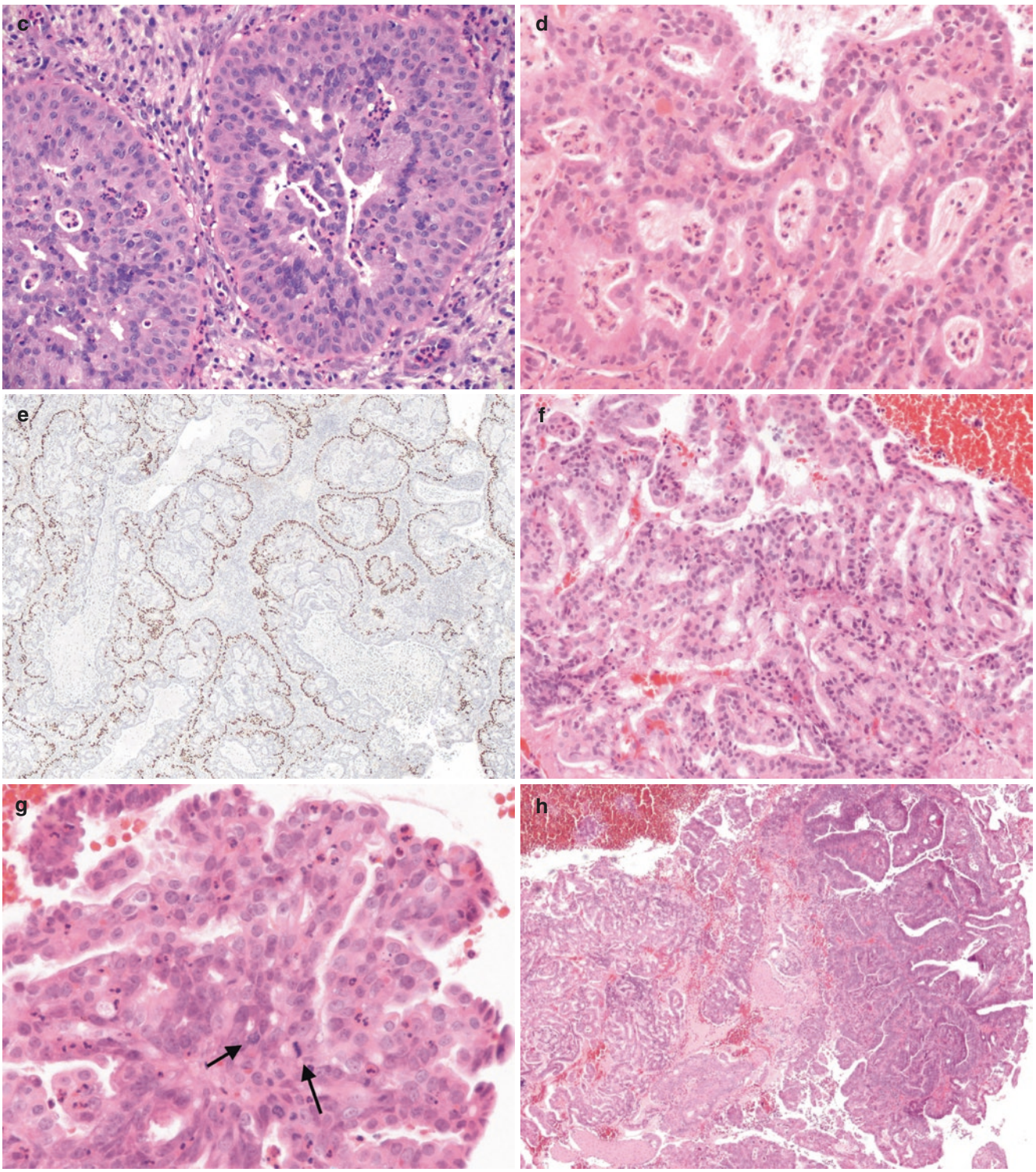

Fig. 3.5 (continued)

3.8 Lobular Endocervical Glandular Hyperplasia (LEGH)

3.8.1 Definition

A benign proliferation of endocervical glands, that can sometimes be associated with adenoma malignum (minimal deviation adenocarcinoma of mucinous type) and gastric type adenocarcinoma of the cervix [41]. The term "florid endocervical glandular hyperplasia with pyloric and intestinal metaplasia" has been used in the past [42].

3.8.2 Etiology

A minority of cases can be found in association with Peutz-Jeghers syndrome [43].

3.8.3 Macroscopy

Typically, LEGH is not macroscopically visible, although exceptions occur.

3.8.4 Microscopy

There is an exuberant proliferation of endocervical glands with a lobular architecture. In many cases, the lobular proliferations contain a central dilated duct-like gland, as there are no true ducts in the cervix. LEGH is usually confined to the inner half of the cervical wall and there is no stromal desmoplasia. The endocervical glands are composed of columnar cells with pale eosinophilic cytoplasm and basally located nuclei. The eosinophilic cytoplasm contrasts with the more basophilic cytoplasm of normal endocervical glands [44]. LEGH contains neutral mucin, akin to gastric foveolar epithelium, but not acidic mucin, which is present in normal endocervical glands. This neutral mucin will stain magenta with Alcian blue/PAS combination stain; normal endocervical glands stain purple-violet. Rare goblet cells and neuroendocrine cells can be seen.

Atypical LEGH is characterized by the presence of nuclear atypia (nuclear enlargement, hyperchromasia, nucleoli, occasional mitoses and apoptotic debris). They also tend to exhibit a greater degree of epithelial infoldings (papillary projections) and exfoliation of cells into gland lumens. These changes can also be seen in gastric-type adenocarcinoma in situ.

LEGH is positive for HIK1083 and MUC6, and is usually negative for ER and PR [44]. Half of LEGH harbour genetic mutations (*GNAS*, *KRAS*, *STK11*) which supports their preneoplastic nature, rather than a purely metaplastic process [45].

Diagnostic Highlights

- Lobular proliferation of endocervical glands; each lobule often contains a central duct-like gland.
- The cells have ample eosinophilic cytoplasm and basally located nuclei. The cytoplasm contains neutral mucin (in contrast to acidic mucin in normal endocervical glands) and stains magenta with Alcian blue/PAS.
- LEGH is also positive for HIK1083.
- Often found in association with minimal deviation and gastric type adenocarcinomas of the cervix.

3.8.5 Differential Diagnosis

- LEGH can be distinguished from *minimal deviation adenocarcinoma/gastric-type adenocarcinoma* by lobular contours in the former and an irregular glandular proliferation, usually penetrating more deeply into the cervical wall in the latter (see Chap. 8). These adenocarcinomas are usually associated with at least focal stromal desmoplasia and/or nuclear enlargement relative to LEGH.
- *Diffuse laminar endocervical glandular hyperplasia* is another benign glandular proliferation in the cervix. It tends to involve the inner third of the cervix and have a sharp demarcation with the underlying cervical stroma. The glands can be round or branching and the stroma often contains chronic inflammatory cells [46].

3.8.6 Prognosis

LEGH is benign, however, adjacent malignancy such as minimal deviation adenocarcinoma/gastric type adenocarcinoma should be rigorously excluded.

Case A 58-year-old woman had a hysterectomy for fibroids. A glandular proliferation in the cervix was identified (Fig. 3.6).

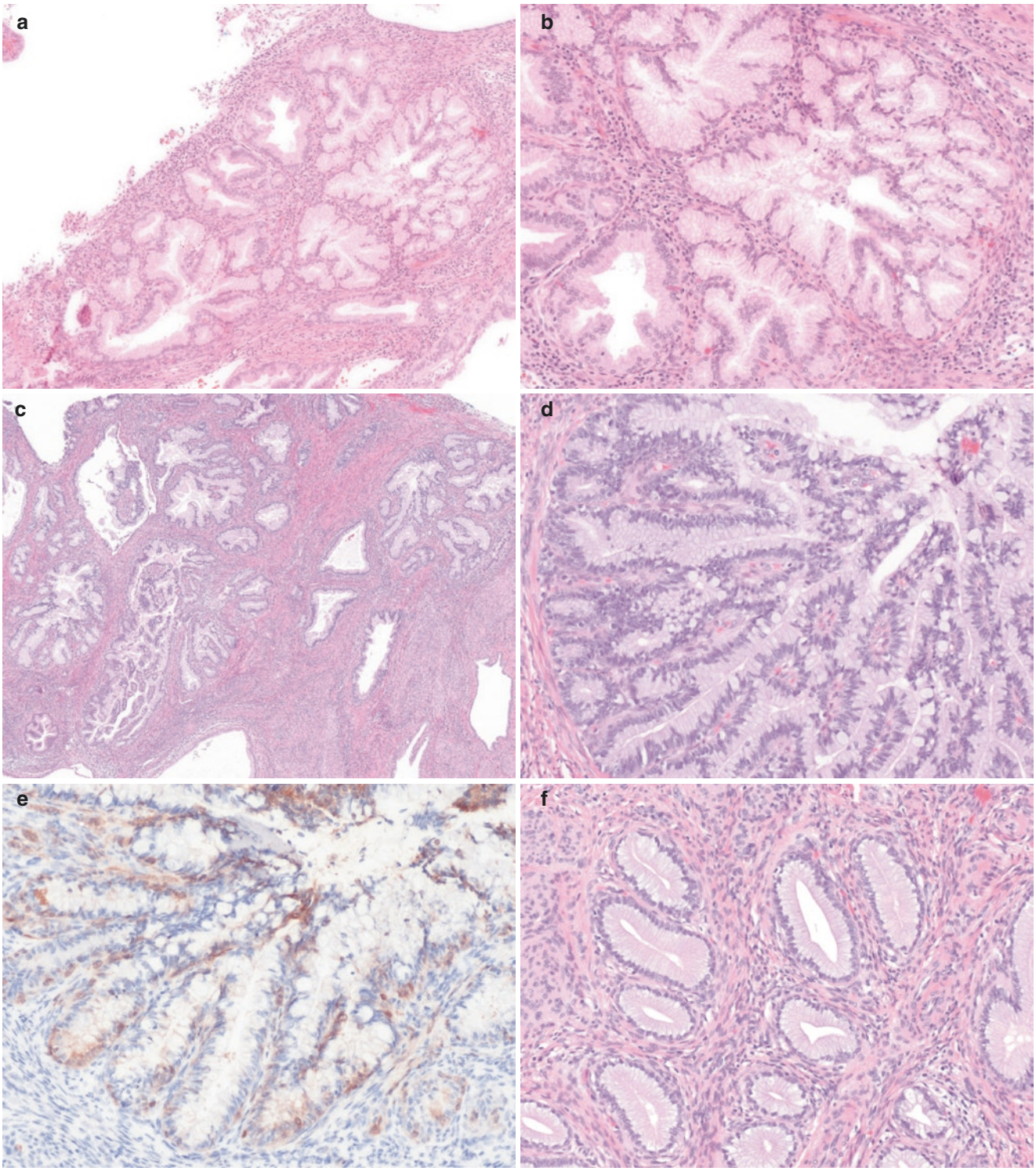

Fig. 3.6 Lobular endocervical glandular hyperplasia. *Case history:* A 58-year-old woman had a hysterectomy for fibroids. A glandular proliferation in the cervix was identified. (**a**) Low-power view of the cervix shows an exuberant proliferation of mucinous glands, with lobular architecture. (**b**) High-power view shows mucinous cells with basally located nuclei without nuclear atypia. For comparison, another patient had atypical glandular cells on PAP smear. A LEEP and hysterectomy was performed: (**c**) The cervix contains a mucinous proliferation where there is lobular architecture and some papillary infoldings. (**d**) There is nuclear enlargement, coarse chromatin and scattered mitoses, in keeping with atypical lobular endocervical glandular hyperplasia (ALEGH). (**e**) p16 is negative, showing patchy weak staining. (**f**) Adjacent areas in the cervix show pyloric metaplasia. The nuclei are bland and basically located, and the cytoplasm is abundant and eosinophilic, similar to the appearance of gastric foveolar epithelium

3.9 Tunnel Clusters

3.9.1 Definition

Tunnel clusters are benign lobular proliferations of endocervical glands.

3.9.2 Etiology

The strong association with multiparity suggests that this finding represents involution of pregnancy-related endocervical glandular hyperplasia. It is found in 10% of women [47].

3.9.3 Macroscopy

Tunnel clusters are an incidental finding that are usually not macroscopically visible.

3.9.4 Microscopy

There are two main forms, a non-cystic type (type A) and a cystic type (type B) [47, 48]. The more common cystic type consists of a lobular aggregate of round, closely packed mucinous glands lined by a single attenuated layer of cuboidal cells with basally located nuclei (see Fig. 3.7). The non-cystic type consists of smaller glands lined by cuboidal or columnar cells. It is usually superficial in the cervical wall. Nuclei are small and bland; mitoses are absent. There is no stromal desmoplasia.

Diagnostic Highlights

- Lobular aggregates of cytologically bland mucinous glands, which can be non-cystic (type A) or cystic (type B)

3.9.5 Differential Diagnosis

Minimal deviation adenocarcinoma (MDA) can also have a bland appearance, but it has irregularly sawtooth-shaped glands and can be associated with a desmoplastic response (see Chap. 8). MDA also lacks the organized lobular arrangement seen in tunnel clusters. Tunnel clusters are uniformly ER/PR positive, whereas most MDAs are ER/PR negative. Loss of PAX2 staining can help favor a malignant glandular lesion [49].

3.9.6 Prognosis

Benign.

Case A 37-year-old gravida 2 para 2 woman had a hysterectomy for pelvic pain (Fig. 3.7).

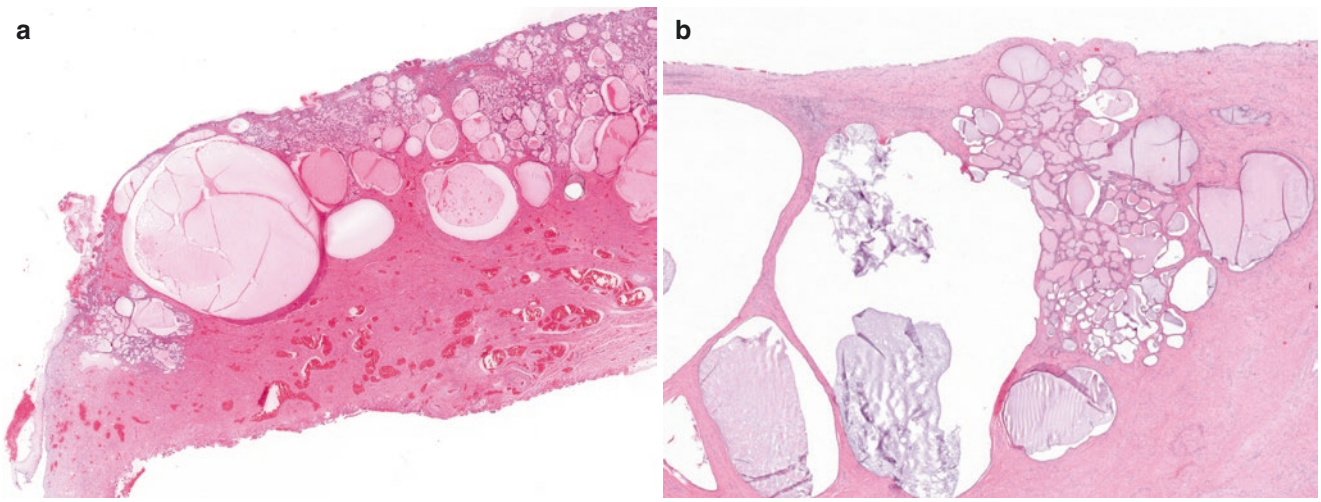

Fig. 3.7 Tunnel clusters, deep glands, and Nabothian cysts. *Case history:* A 37-year-old gravida 2 para 2 woman had a hysterectomy for pelvic pain. (**a**) Low-power view shows large Nabothian cysts and numerous crowded mucinous glands. (**b**) Nabothian cysts (*left*) are seen adjacent to type B (cystic) tunnel clusters (*right*). (**c**) These type A (non-cystic) tunnel clusters are made of crowded small glands. The mucinous cells are often flat. (**d**) These type B tunnel clusters are made of large, dilated mucinous glands. Again, the mucinous cells are attenuated or flat in many areas. (**e**) In areas where the mucinous cells are not flattened, they show basally located nuclei and bland nuclear features. (**f**) In a different patient, benign endocervical glands, which are cystically dilated and contain mucinous secretions, are found in the deep outer third of the cervix. They are close to the paracervical adipose tissue. The appearance overlaps with "endocervicosis" (see following section)

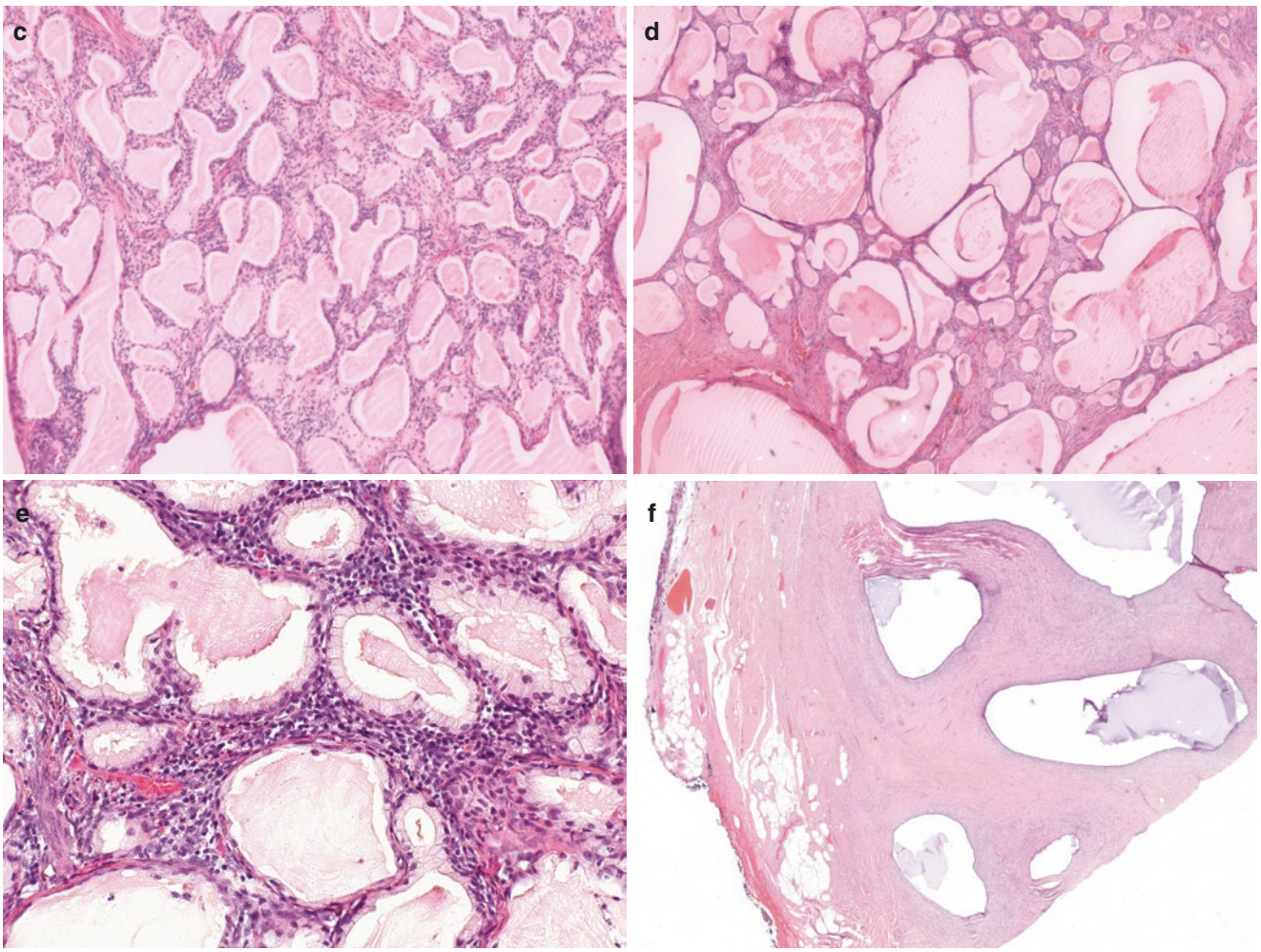

Fig. 3.7 (continued)

3.10 Deep Glands and Nabothian Cysts

3.10.1 Definition

Histologically normal endocervical glands or cysts (Nabothian cysts) are located in the deep (outer third) cervical wall (see Fig. 3.7a, b, f).

3.10.2 Etiology

These are a variant of normal anatomy.

3.10.3 Macroscopy

The outer wall of the cervix is enlarged, rubbery, and can form a mass-like lesion. On cut section, the cysts are macroscopically visible.

3.10.4 Microscopy

Widely spaced, bland endocervical glands lack cytologic atypia and mitoses [50]. The glands or cysts can extend into the outer third of the cervical wall and occasionally into the paracervical tissues [51]. There can be admixed Müllerian-type glands (i.e., endometrial glands) and endometrial stroma.

Diagnostic Highlights

- Benign endocervical glands found deep within the cervical stroma or even in the paracervical tissues

3.10.5 Differential Diagnosis

- The wide spacing of the glands, their relatively uniform shape and size, and the absence of nuclear atypia and periglandular stromal response can help distinguish this

from *minimal deviation adenocarcinoma (MDA)* (see Chap. 8). There can be a stromal response to extravasated mucin, which should not be confused with desmoplasia seen in MDA [52].

- *Endocervicosis* is the finding of benign endocervical glands outside of the female reproductive tract, such as the bladder, rectum and bowel. It is thought to be related to displacement of endocervical cells due to previous surgery. The benign endocervical glands can be found in association with tubal-type and endometrial-type glands and is alternatively called Müllerianosis (Fig. 3.8).

3.10.6 Prognosis

Benign.

Case A 37-year-old woman presented with pelvic pain and subsequent imaging revealed a cystic lesion in the bladder. A bladder biopsy was performed (Fig. 3.8).

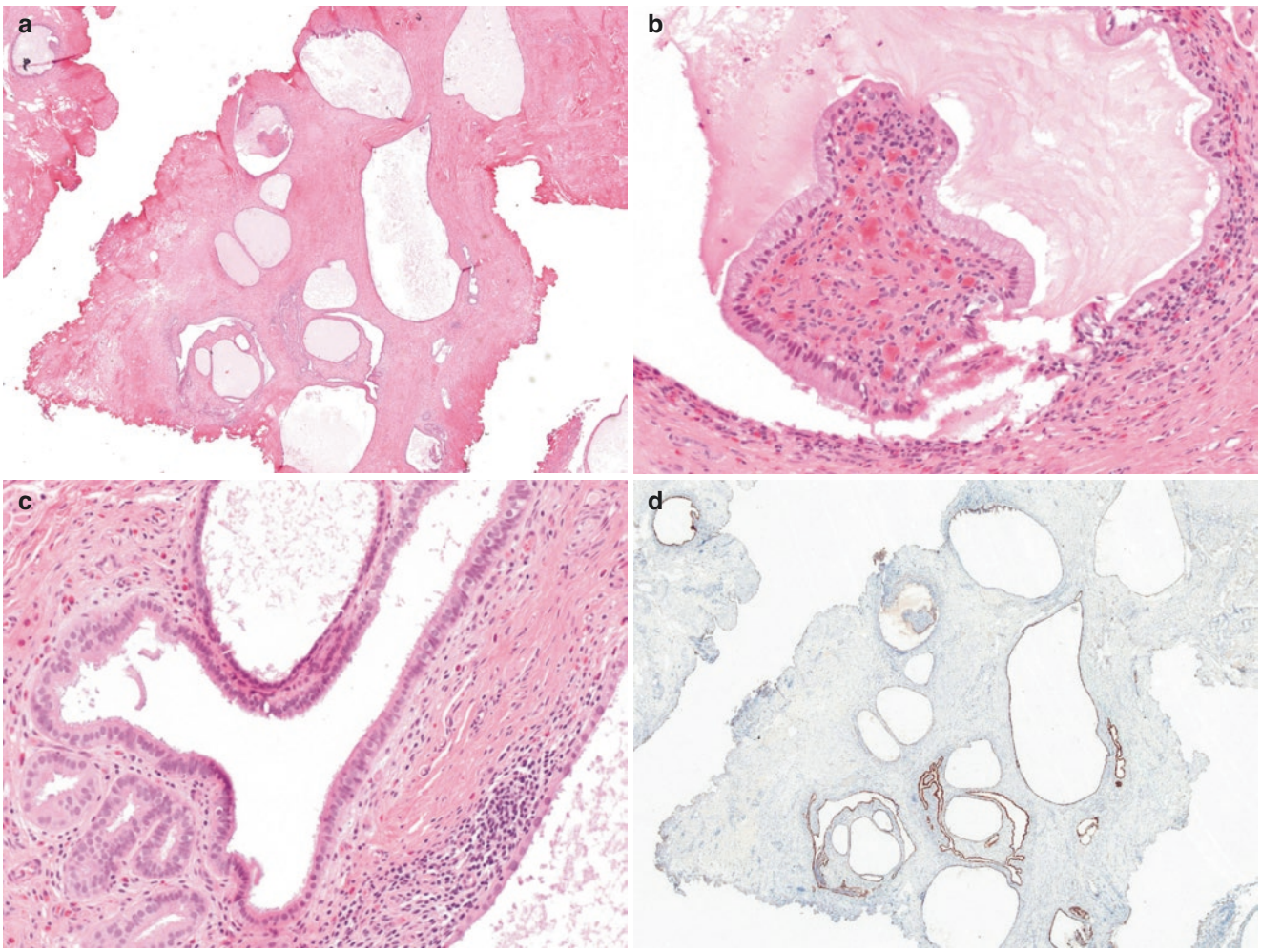

Fig. 3.8 Endocervicosis/Müllerianosis. *Case history:* A 37-year-old woman presented with pelvic pain and subsequent imaging revealed a cystic lesion in the bladder. A bladder biopsy was performed. (**a**) The bladder biopsy shows multiple cystic lesions within the bladder muscularis propria. (**b**) Many cysts are lined by columnar mucinous cells with banal cytology, similar to the appearance of benign endocervical glands (endocervicosis). (**c**) Other cysts are lined by tubal type epithelium. (**d**) ER is positive in the mucinous and tubal type areas in keeping with Müllerianosis

3.11 Mesonephric Remnants and Hyperplasia

3.11.1 Definition

Mesonephric remnants are vestigial remnants of the Wolffian/mesonephric ducts (embryologic male reproductive tract).

3.11.2 Macroscopy

Mesonephric remnants do not form masses and thus are not grossly apparent. Very rarely, mesonephric hyperplasia can be associated with thickening or friability of the cervix, or a mass lesion [53, 54].

Diagnostic Highlights

- Remnants of mesonephric duct often found deep within the cervical wall
- Two major forms: tubular (small round tubules with cuboidal cells) and ductal (glands with columnar cells and sometimes angulated contours)
- Cytology is bland and cells lack cilia, mucin and squamous differentiation
- Positive for PAX8, GATA3 and CD10 (luminal staining), negative for ER
- Mesonephric hyperplasia has 3 patterns: tubular-lobular, tubular-diffuse and ductal. It lacks *KRAS* mutations, unlike the majority of mesonephric carcinomas

3.11.3 Microscopy

Mesonephric remnants are found in up to 30% of uteri, typically in the lateral (9 o'clock and 3 o'clock) walls of the cervix [55, 56]. Remnants are usually situated deep in the cervical wall, but they can be more superficial. Mesonephric remnants may have two patterns: tubular and ductal. The tubular pattern comprises small to medium-sized tubules lined by bland cuboidal cells. They are filled with dense eosinophilic secretions that are PAS and mucicarmine positive (Fig. 3.9). The ductal pattern comprises ducts of larger diameter, with angulated contours; these lack eosinophilic secretions and are lined by cuboidal or columnar cells. The ductal pattern can have tubules at its periphery. The cells lack cilia, mucin, and squamous differentiation. Nuclei are small and bland; some show nuclear grooves. Mitotic activity is absent or rare. The distinction between mesonephric remnants and hyperplasia is arbitrary, with a proposed cutoff value of 6 mm [57]. There are three patterns of mesonephric hyperplasia: tubular-lobular, tubular-diffuse, and ductal (Fig. 3.10). Desmoplasia is absent [56]. The cells are positive for PAX8, GATA3, CD10 (luminal staining), and calretinin (see Fig. 3.9d, f, g). They are negative for ER (see Fig. 3.9e). p16 shows patchy staining (see Fig. 3.9h), and p53 is wild-type [58–60]. A small series reported that TTF1 is negative in mesonephric remnants [61]. Mesonephric adenomyomas consist of lobules of mesonephric tubules/ducts surrounded by smooth muscle [62]. Mesonephric hyperplasia lacks *KRAS* and *NRAS* mutations [53].

3.11.4 Differential Diagnosis

- *Mesonephric carcinoma* is characterized by tubules or ducts with back-to-back or complex architecture (solid/spindled growth), mitotic activity, cytologic atypia, and desmoplasia [63].
- *Endometrioid endometrial adenocarcinoma* with a deceptively bland pattern of invasion into the cervical stroma can mimic the appearance of mesonephric remnants. Endometrial adenocarcinoma will be ER/PR positive and GATA3 negative; the reverse pattern applies to mesonephric proliferations [64].

3.11.5 Prognosis

Both mesonephric remnants and hyperplasia are benign.

Cases A hysterectomy was performed in a 50-year-old woman with low-grade endometrioid adenocarcinoma. An abnormal proliferation of glands was seen in the cervical stroma (Fig. 3.9).

A 41-year-old woman had a hysterectomy for endometriosis and pelvic pain. Sections of the cervix show a glandular proliferation (Fig. 3.10).

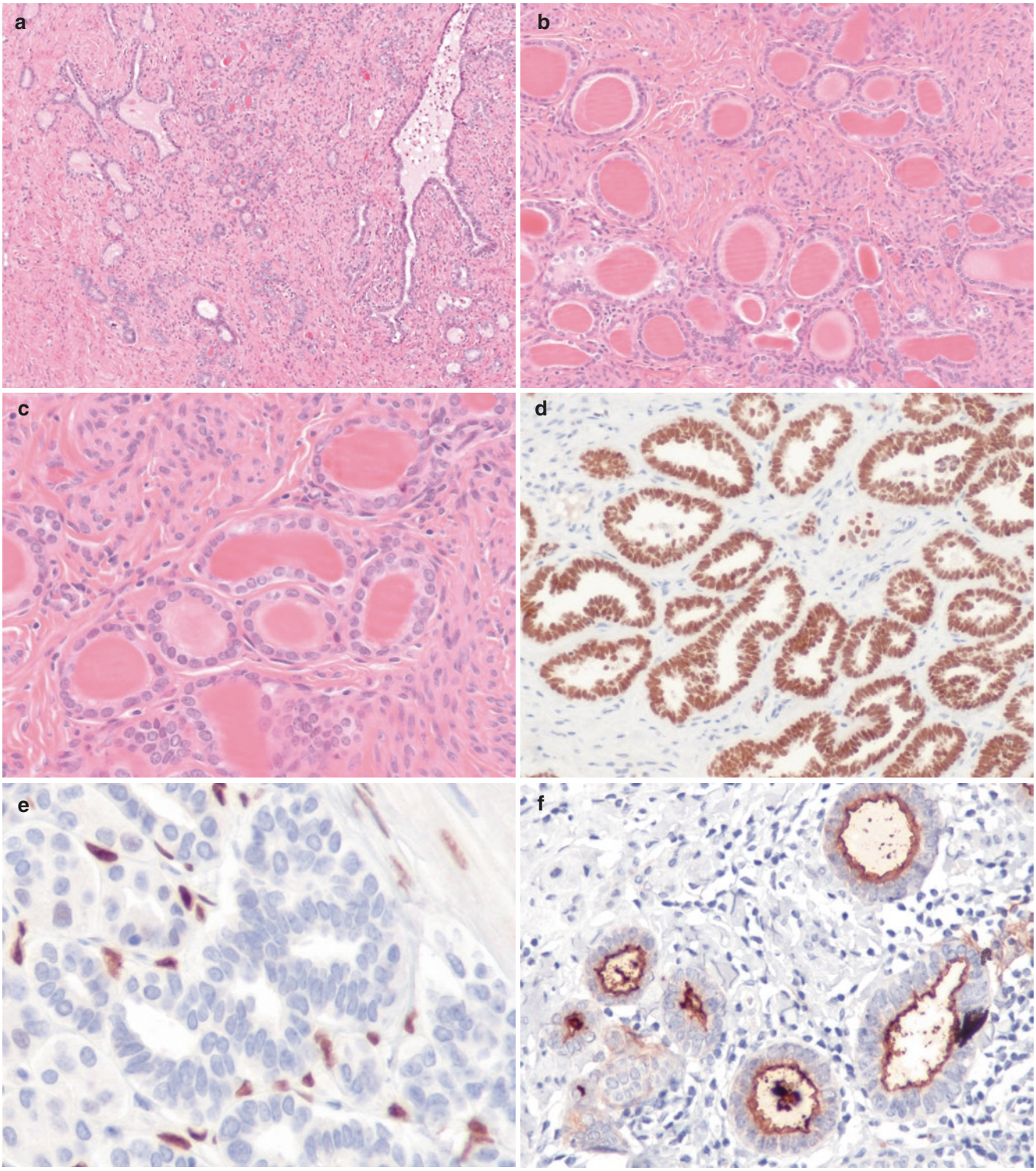

Fig. 3.9 Mesonephric remnants. *Case history:* A hysterectomy was performed in a 50-year-old woman with low-grade endometrioid adenocarcinoma. A proliferation of glands was seen in the cervical stroma, leading to a question of cervical spread of endometrioid adenocarcinoma. These glands in the cervix were found to be mesonephric remnants. (**a**) Examination of the deep cervical wall shows large ducts surrounded by smaller tubules. (**b**) The tubules are filled with dense, eosinophilic secretions. (c) The cells are cuboidal, the nuclei are round, and there is no atypia or mitoses. (**d**) GATA3 is positive. (**e**) ER is negative. (**f**) CD10 shows luminal staining. (**g**) Calretinin is positive. (**h**) p16 shows patchy staining, which is considered negative

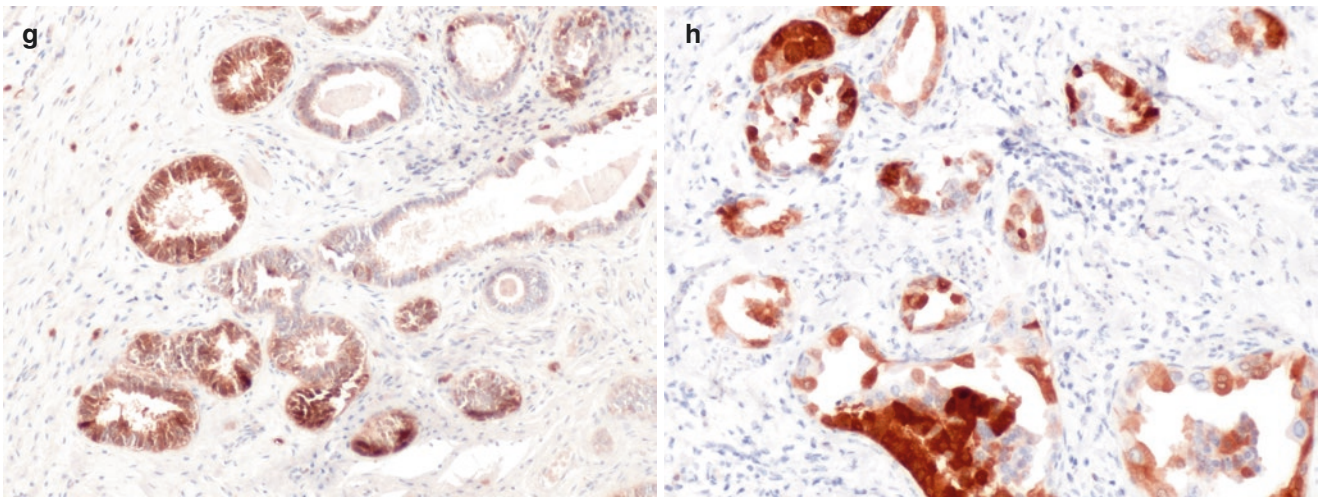

Fig. 3.9 (continued)

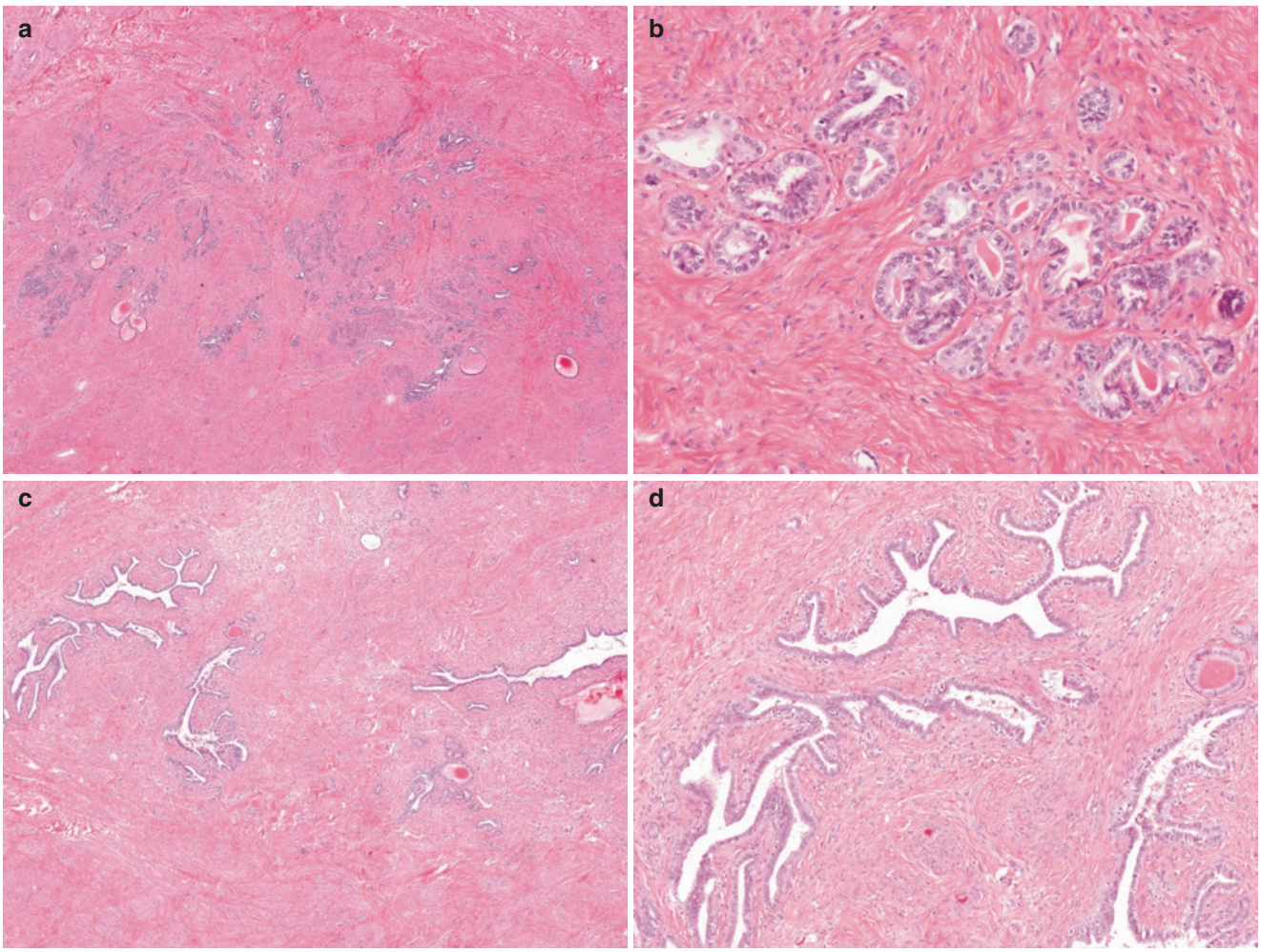

Fig. 3.10 Mesonephric hyperplasia. *Case history:* A 41-year-old woman had a hysterectomy for endometriosis and pelvic pain. Sections of the cervix show a glandular proliferation. (**a**) The glands/tubules exhibit lobular architecture, some lobules contain central ducts. (**b**) Each lobular proliferation contains small tubules with cuboidal cells, bland cytology and dense eosinophilic secretions. (**c**) A different case shows a proliferation of angulated ducts within the deep cervical wall. (**d**) The ducts have sharply angulated contours and are lined by similar bland cuboidal cells

3.12 Inflammatory (Non-infectious) Processes

3.12.1 Definition

Inflammation of the cervix can be related to non-infectious processes.

3.12.2 Etiology

Inflammation of the cervix can be related to the normal cervical environment, which protects the uterine cavity from ascending infection, or it can be due to inflammatory diseases.

3.12.3 Microscopy

Papillary endocervicitis The cervical mucosa appears papillary (Fig. 3.11). The papillae contain an admixture of chronic inflammatory cells, and the papillae are lined by a single layer of bland, columnar mucinous epithelium. This appearance may mimic villoglandular endocervical adenocarcinoma, which is also superficial and papillary, but the adenocarcinoma shows nuclear atypia, mitoses, apoptotic bodies, and diffuse p16 staining.

Follicular endocervicitis and florid reactive lymphoid hyperplasia This chronic inflammatory infiltrate can also have lymphoid follicles. The inflammation remains superficial and the lymphocytes are polyclonal, which can be confirmed by immunohistochemical or molecular studies. Care should be taken to exclude a lymphoma (presence of a cervical mass, deep inflammation, prominent sclerosis, monoclonality) and an underlying infection (such as chlamydia) [65, 66].

Histiocytic and xanthogranulomatous inflammation Lipogranulomas and necrobiotic granulomas can form secondary to prior surgery or pyometra [67]. Rarely, histiocytic inflammation can be due to malacoplakia [68, 69].

Ligneous cervicitis is due to inherited type 1 plasminogen deficiency. There is denudation of the surface epithelium, pseudomembranes (dense neutrophilic infiltrate), and deposition of amorphous eosinophilic material. This material can resemble amyloidosis but will be positive for antifibrinogen immunohistochemistry and negative for Congo red [70, 71].

Vasculitis is usually an incidental finding in the gynecologic tract, but sometimes it can represent a systemic vasculitis such as giant cell arteritis, polyarteritis nodosa, granulomatosis with polyangiitis (Wegener's granulomatosis), or Behçet's disease. Arterioles or small arteries can exhibit lymphocytic, necrotizing, or granulomatous inflammation [72–75].

3.12.4 Differential Diagnosis

Plasma cells are frequent constituents of the chronic inflammatory infiltrate of the endocervix. During an endometrial curettage, fragments of endocervix containing plasma cells may be sampled and should not be misinterpreted as chronic endometritis.

3.12.5 Prognosis

Benign.

Case This 45-year-old woman had a hysterectomy for pelvic pain. Review of the clinical chart shows that swabs taken during her recent Pap smear were negative for infections (Fig. 3.11).

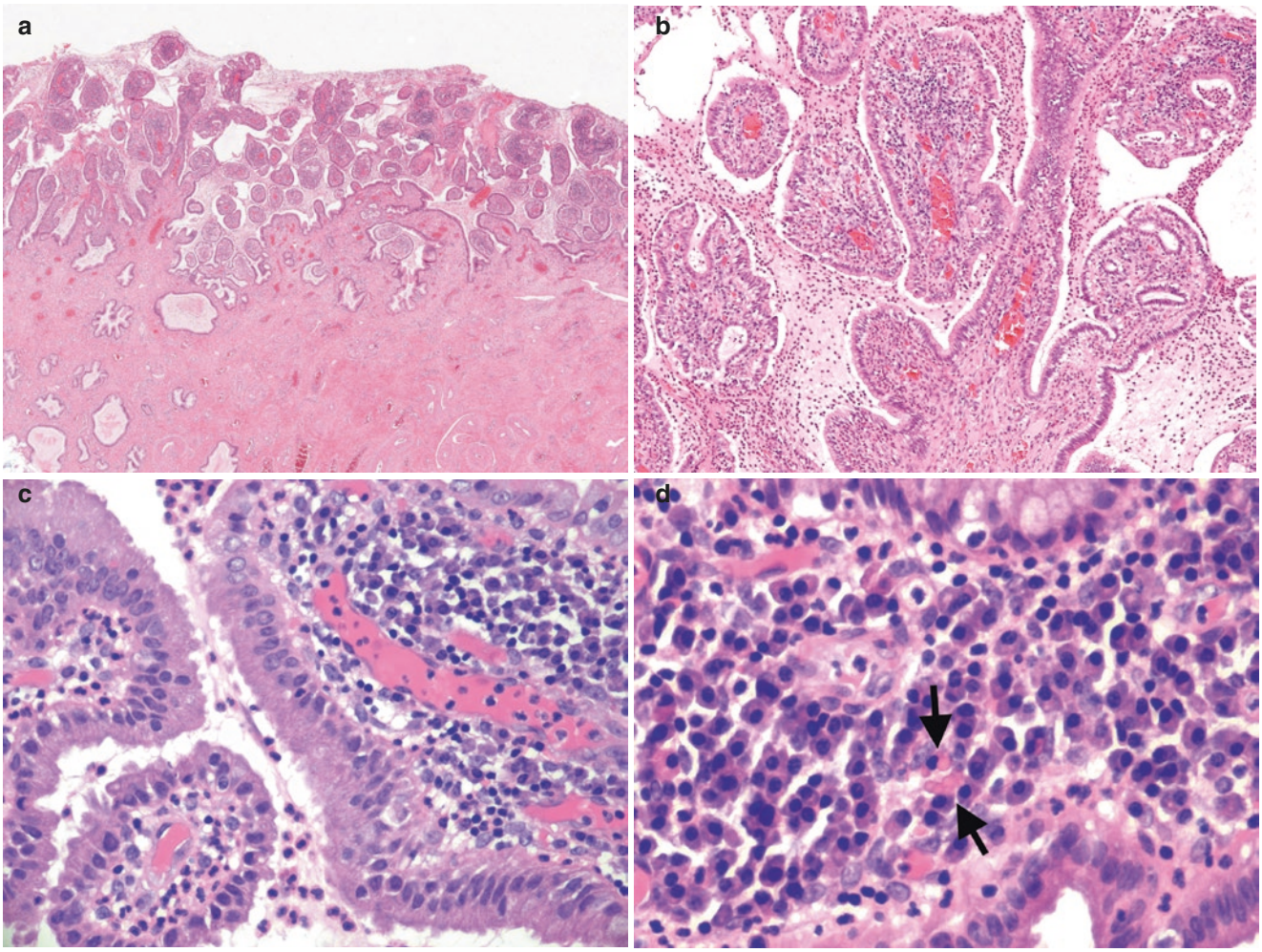

Fig. 3.11 Papillary endocervicitis. *Case history:* This 45-year-old woman had a hysterectomy for pelvic pain. Review of the clinical chart shows that swabs taken during her recent Pap smear were negative for infections. (**a**) Low-power view of the cervix shows a papillary proliferation involving the cervical mucosa. It has a smooth interface with the underlying cervical stroma. (**b**) The papillary structures are each lined by a single layer of mucinous cells. There is a background of mucus containing inflammatory cells. (**c**) The mucinous cells lining each papilla have basally located nuclei and open chromatin. (**d**) The stroma contains mixed inflammatory cells, enriched in plasma cells. Focal Russell bodies can be seen (black arrows)

3.13 Infections

3.13.1 Definition

A variety of viral, bacterial, mycobacterial, fungal, or protozoal organisms can infect the cervix.

3.13.2 Etiology

Infections of the cervix often represent the initiating site for pelvic inflammatory disease. Types of cervix infection vary worldwide by geography and patient immune status. Chlamydia and gonorrhea are the most common bacterial infections, cytomegalovirus (CMV) is more common in immunocompromised patients, and schistosomiasis is frequent in parts of Africa and South America.

A 21-year-old woman was found to have atypical squamous cells of undetermined significance (ASC-US) on a Pap smear. She subsequently underwent a colposcopy and cervical biopsy (Fig. 3.12).

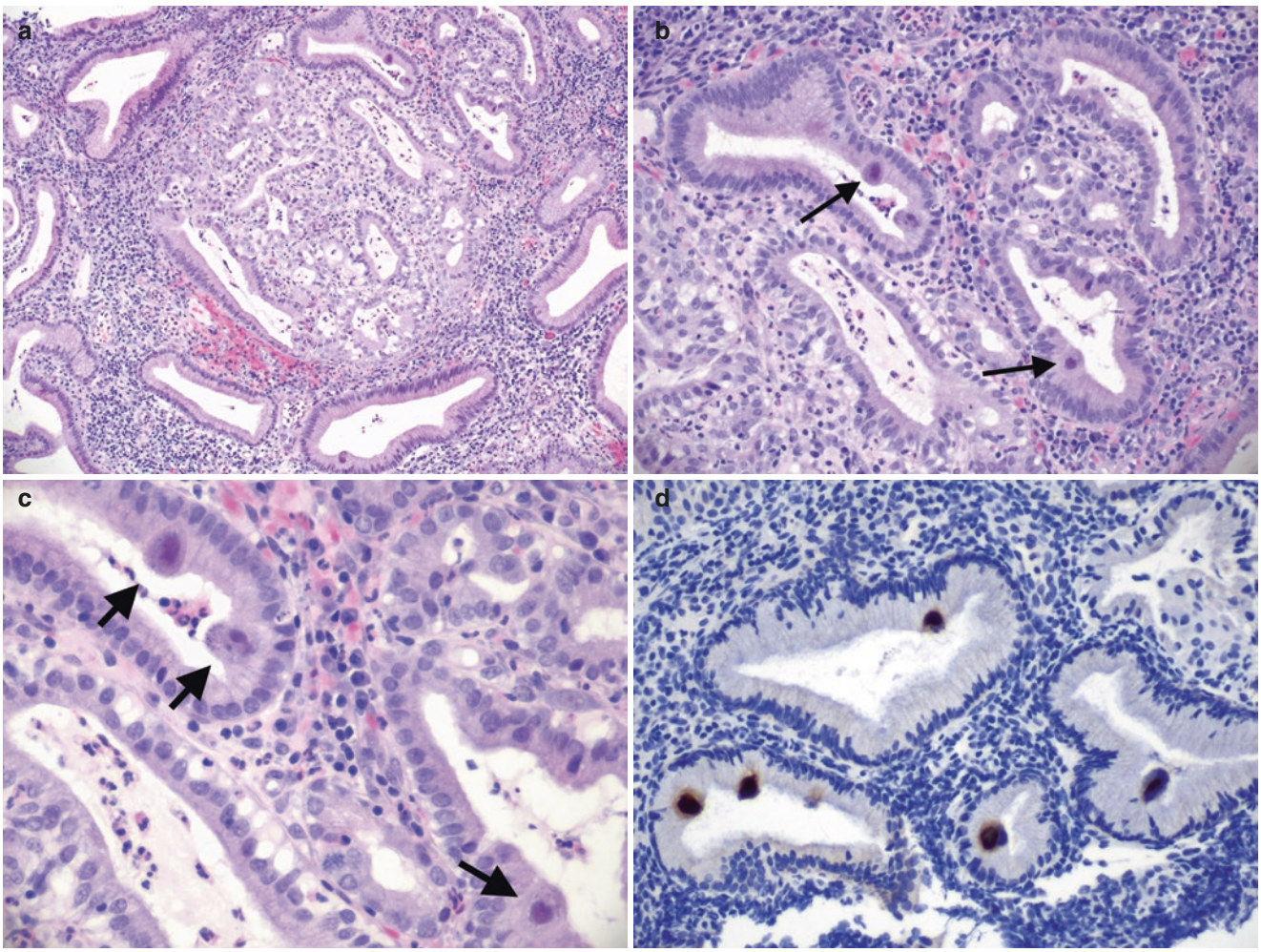

Fig. 3.12 Cytomegalovirus. *Case history:* A 21-year-old woman was found to have atypical squamous cells of undetermined significance (ASC-US) on a Pap smear. She subsequently underwent a colposcopy and cervical biopsy. (**a**) The endocervical biopsy shows benign endocervical glands with microglandular hyperplasia. (**b**) Rare enlarged hyperchromatic cells are identified. (**c**) On high power, the cells contain eosinophilic intranuclear inclusions. (**d**) Immunohistochemistry for cytomegalovirus (CMV) is positive. The finding of CMV in a cervical biopsy has uncertain clinical implications for the patient, but vertical transmission to a future fetus can result in neonatal complications such as CMV growth restriction, chorioretinitis, periventricular cerebral calcifications, and deafness

3.13.3 Macroscopy

Lesions may appear erythematous, friable, mucopurulent (chlamydia and gonorrhea), or ulcerative; may form a mass (tuberculosis); or may appear clinically normal (occult infection).

3.13.4 Microscopy

Chlamydia trachomatis There is a diffuse, chronic inflammatory infiltrate, often with lymphoid follicles (follicular cervicitis) [76].

Neisseria gonorrhoeae Diffuse suppurative inflammation is typical.

Tuberculosis Necrotizing granulomas are made of epithelioid histiocytes and multinucleated Langhans giant cells. Acid-fast bacilli are highlighted by a Ziehl-Neelsen stain. Effective treatment can result in complete resolution of the granulomas [77].

Cytomegalovirus Cytoplasmic and nuclear basophilic or amphophilic inclusions are seen in endothelial and stromal cells, and occasionally in glandular epithelial cells (see Fig. 3.12c). Squamous cells are usually not affected. There can be associated fibrin thrombi and a dense inflammatory infiltrate [78] (Fig. 3.12).

Schistosomiasis Ova (which are often calcified) are surrounded by multinucleated giant cells and noncaseating granulomas. Some cases may also contain eosinophils. There are rare case reports of schistosomiasis occurring with cervical squamous cell carcinoma [79, 80].

Examples of other infections that can occur include actinomycosis, *Candida albicans*, herpes simplex virus, syphilis, and trichomonas. Human papillomavirus, a common infection of the cervix, is covered elsewhere. The microorganisms themselves may not be apparent on histologic examination and will require correlation with microbiological cultures and investigations.

3.13.5 Differential Diagnosis

- Some infections, particularly in immunocompromised (HIV-positive) patients, can result in a mass or tumor-like lesion that can mimick the appearance of cancer.

3.13.6 Prognosis

In pregnant women, cervical infections may lead to spontaneous abortion, premature delivery, chorioamnionitis, stillbirth, and neonatal complications.

3.14 Arias-Stella Reaction

3.14.1 Definition

The Arias-Stella reaction (ASR) is a reactive glandular change associated with pregnancy and hormonal treatment (*ie*, high-dose progestins, oral contraceptives).

3.14.2 Etiology

ASR is found in up to 10% of hysterectomy specimens from pregnant patients [81]. Reported patients have ranged from 19 to 44 years of age [82].

3.14.3 Macroscopy

ASR is an incidental finding that is not macroscopically visible. It can also be found incidentally within an endocervical polyp (Fig. 3.13) [83].

3.14.4 Microscopy

The original description by Javier Arias-Stella included five major patterns: minimal atypia, early secretory, secretory/hypersecretory, regenerative/nonsecretory, and monstrous [83]. Most involve scattered superficial glands, although involvement of deep glands and diffuse gland involvement can be seen. Glands have intraglandular tufts or filiform papillae and occasional cribriforming [82]. Cells are hobnail with vacuolated, voluminous, clear, or oxyphilic cytoplasm. Nuclei can be enlarged, irregular, hyperchromatic, and pyknotic. Nuclear pseudoinclusions impart an optically clear or smudged appearance. There is a spectrum of atypia in which bland, normal-appearing cells are interspersed between the atypical cells [84]. Usually there are few or no mitotic figures, and Ki-67 is low [85]. Nearly all cases are ER positive [84, 86].

Diagnostic Highlights

- Benign finding often seen in pregnancy or high-dose progestational treatment
- Glands with hobnail cells, vacuolated and voluminous clear/oxyphilic cytoplasm
- Nuclei can be enlarged, irregular, hyperchromatic, pyknotic and bear optically clear pseudoinclusions
- There are few or no mitotic figures, and Ki-67 is low
- Nearly all cases are ER positive, although the intensity of ER can be attenuated

3.14.5 Differential diagnosis

- Arias-Stella reaction can be confused with *clear cell carcinoma*. In ASR, mitotic figures will be absent or rare, highly atypical nuclei will be absent, and ER will be positive. The finding of normal cells interspersed between atypical cells can be helpful. The finding of a mass lesion, stromal invasion, tubulocystic and solid architecture, and hyalinized cores strongly favors a diagnosis of clear cell carcinoma.
- In comparison to the background normal endocervical glands, ASR can have attenuated ER staining and rare cases are ER negative. The attenuated ER staining pattern should not be considered an indicator of clear cell carcinoma [83, 84]. Napsin A, hepatocyte nuclear factor-1-beta (HNF-1β), and cystathionine gamma-lyase (CTH) are positive in both ASR and clear cell carcinoma and will not distinguish between the two [84, 86].

3.14.6 Prognosis

Benign.

Case This endocervical polyp was removed from a 31-year-old woman who was 12 weeks pregnant (Fig. 3.13).

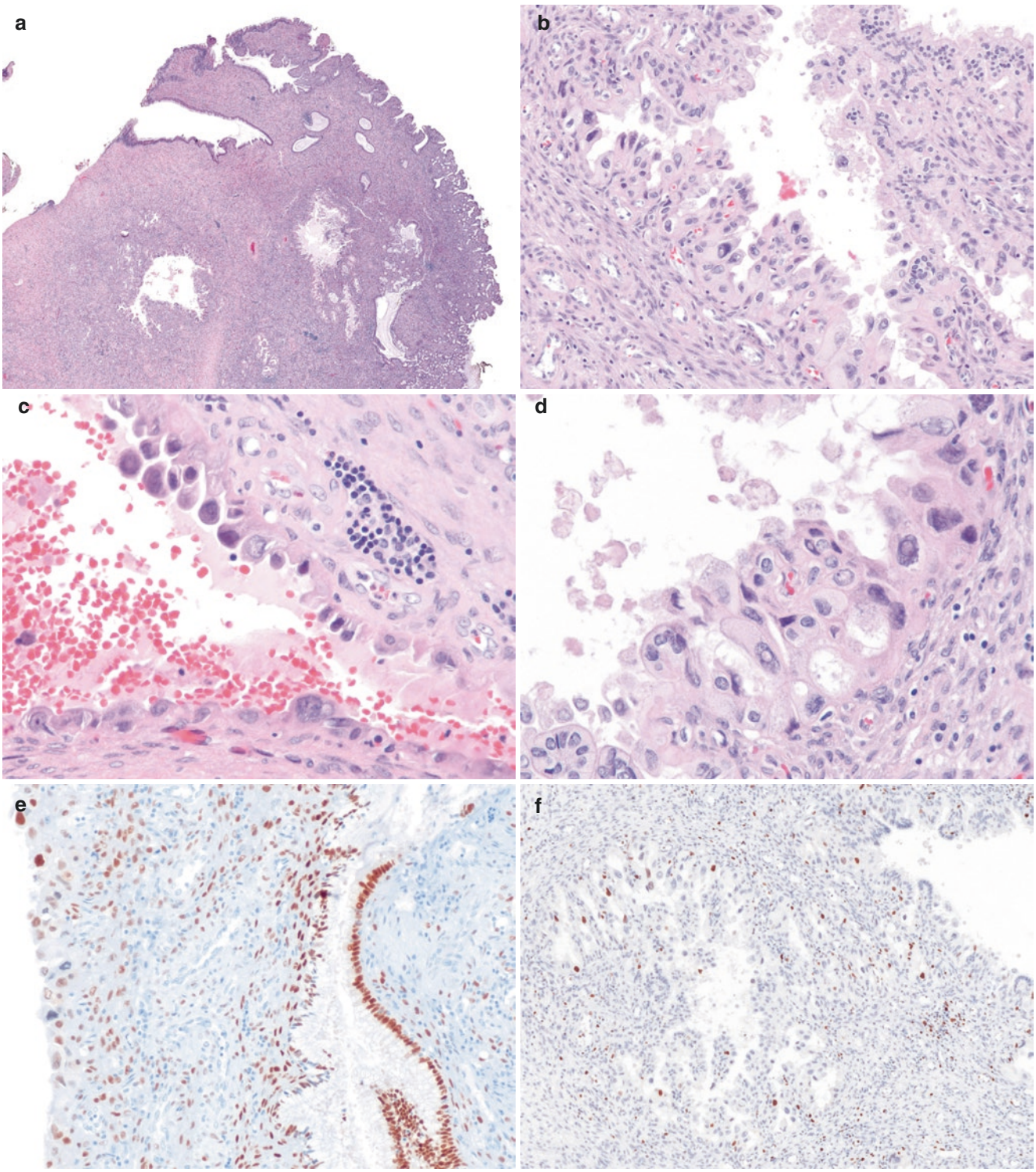

Fig. 3.13 Arias-Stella reaction. *Case history:* This endocervical polyp **(a)** was removed from a 31-year-old woman who was 12 weeks pregnant. (**b**) The endocervical polyp shows atypical cells within its center and the glands have small intraluminal papillations. (**c**) The nuclei are enlarged and the chromatin is hyperchromatic and smudgy. Some nuclei are pale and contain intranuclear inclusions. The cytoplasm is pale to clear. (**d**) Other areas show hobnail cells containing large, hyperchromatic nuclei. (**e**) The cells are positive for ER, although the intensity is less than that seen in the normal endocervical glands (*right*). (**f**) Ki67 shows a low proliferation index. (**g**) Napsin is positive, with a granular staining pattern. Napsin will not distinguish between Arias-Stella reaction and clear cell carcinoma. (**h**) HNF-1β is positive. HNF-1β will not distinguish between Arias-Stella reaction and clear cell carcinoma

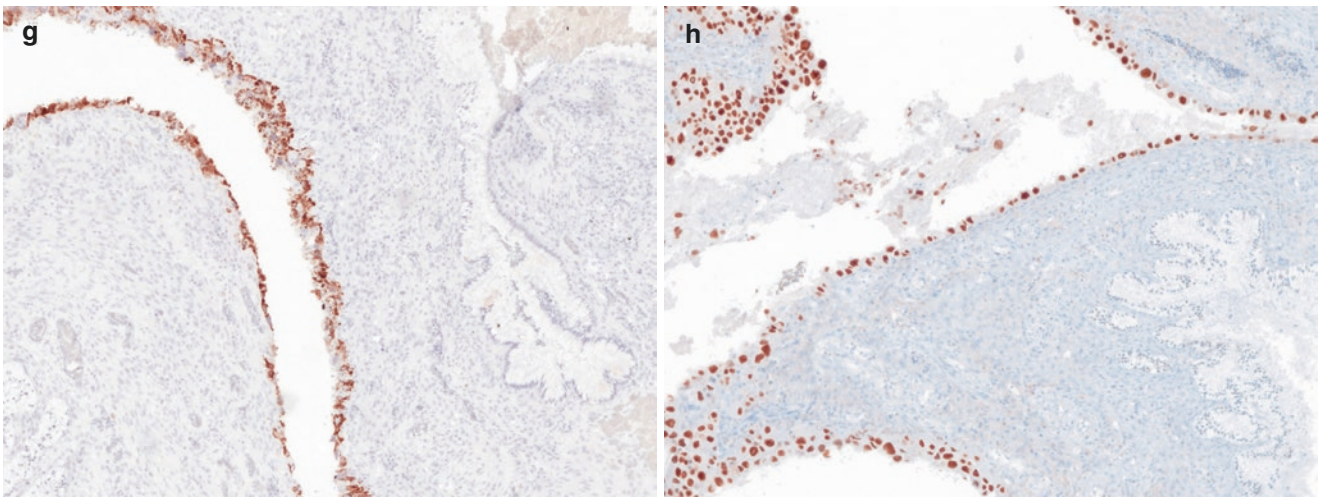

Fig. 3.13 (continued)

3.15 Other Reactive and Reparative Changes

3.15.1 Definition

Reactive and reparative changes can be secondary to mechanical, surgical, or chemical trauma.

3.15.2 Etiology

A variety of changes can occur in response to prior surgical intervention (endocervical or endometrial curettings, cone biopsy, LEEP), mechanical trauma (pessary, diaphragm, intrauterine device), chemical injury, radiation, or childbirth.

3.15.3 Macroscopy

Injury to the cervix can result in red or yellow discolorations, erosions, lacerations, mucosal irregularities, fibrosis, induration, or stenosis.

3.15.4 Microscopy

Reparative changes In epithelial repair, endocervical cells can be mucin-depleted, squamous cells can appear hypereosinophilic, and micropapillary and hobnail cells can be seen (see Fig. 3.14a–d). There can be visible nucleoli and modest pleomorphism, but the chromatin pattern is smooth, and mitoses are sparse and basilar. There is often spongiosis and a heavily inflamed stroma [87].

Uterine prolapse can result in hyperkeratosis, parakeratosis, acanthosis, and pagetoid dyskeratosis. The features can resemble lichen simplex chronicus, as seen in the skin (see Fig. 3.14e, f). In pagetoid dyskeratosis, large cells with pale cytoplasm and pyknotic nuclei can be seen in the suprabasal layers, mimicking koilocytes, extramammary Paget's disease, and pagetoid spread of carcinoma cells to the cervix. These cells are negative for CAM5.2 and epithelial membrane antigen (EMA) [88].

Pseudoinvasion of benign squamous epithelium post-biopsy After a biopsy or LEEP, displacement of squamous epithelium can be confused with invasive squamous cell carcinoma or lymphovascular invasion if there is retraction artifact. The entrapped nests appear hypereosinophilic with associated granulation tissue and a stromal inflammatory response. The focality, bland nuclear features, absence of nearby squamous intraepithelial lesion, and absence of abnormal epithelium between the deep nests and surface epithelium can identify this as pseudoinvasion [89].

Radiation atypia The cells can become enlarged with hyperchromatic nuclei, loss of polarity, prominent nucleoli, and necrosis, but the glands remain well spaced and the N:C ratio of the cells remain low. Smudged chromatin and cytoplasmic vacuolization also can be seen [90].

3.15.5 Prognosis

Benign.

A variety of reactive and regenerative changes can occur in the cervix (Fig. 3.14).

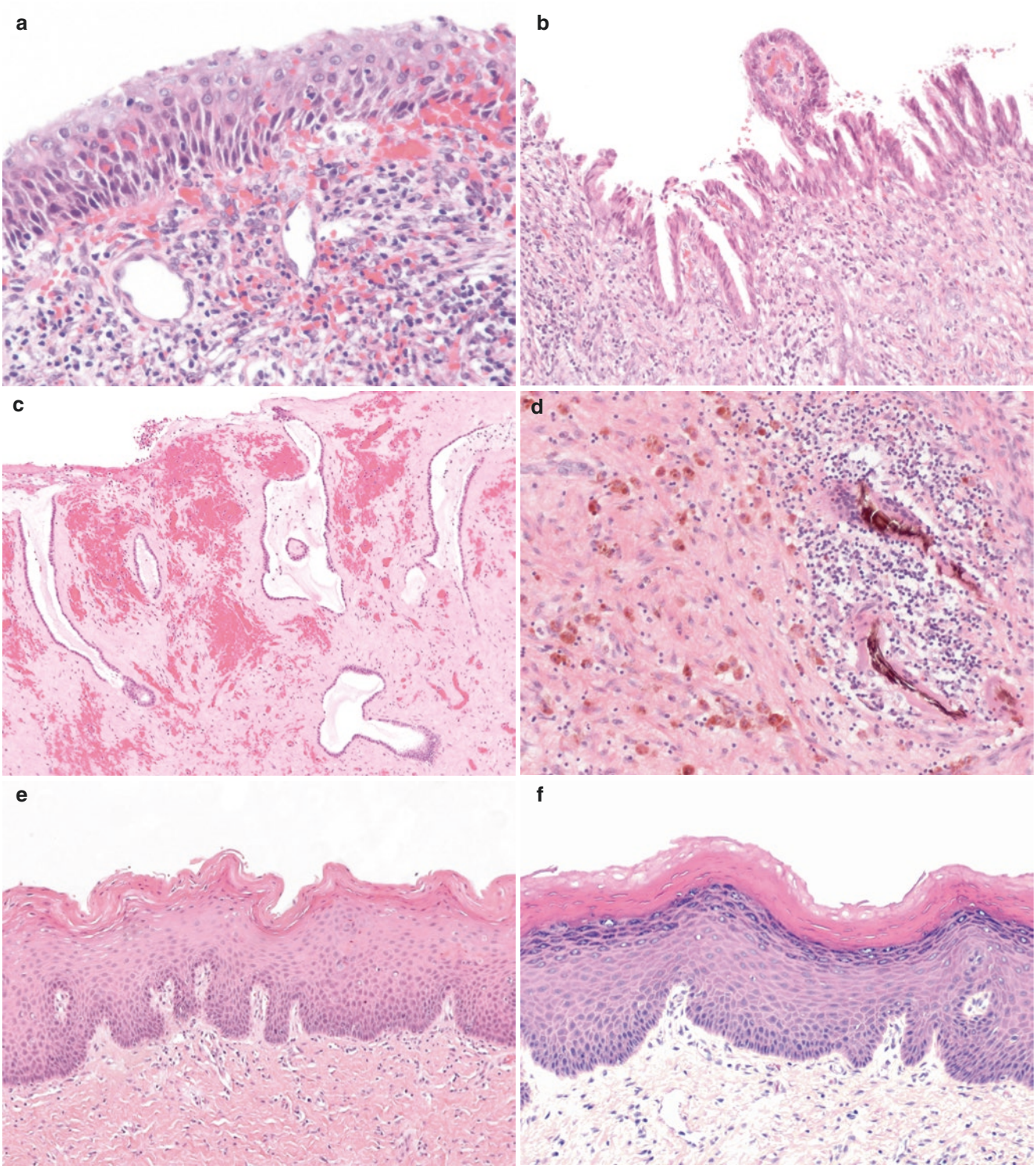

Fig. 3.14 Reparative changes. A variety of reactive and regenerative changes can occur in the cervix. Figs. 3.14a–d represent post-LEEP hysterectomies from different patients. Fig. 3.14e and f are from two postmenopausal patients with uterine prolapse. (**a**) Immature squamous metaplasia is seen. The cells are crowded and organized, without atypia. Underlying vascular ectasia and stromal inflammatory cells are also seen. (**b**) The reactive endocervical cells form small micropapillae. The cells are mucin-depleted, but the nuclei are still basally located. There are admixed intraepithelial and stromal inflammatory cells. (**c**) The stroma is hyalinized and hemorrhagic. The glands are irregular in size and shape but are still widely spaced. (**d**) Monsel's solution (20% ferric subsulfate) was used for hemostasis and is seen here as brown pigment engulfed by foreign-body giant cells. (**e**) The cervical mucosa shows acanthosis, hyperkeratosis, and parakeratosis. (**f**) Here the cervical mucosa shows compact hyperkeratosis and hypergranulosis. The appearance resembles lichen simplex chronicus seen in the skin

References

1. Reich O, Regauer S. Papillary immature metaplasia and thin high-grade squamous intraepithelial lesion originate in early metaplastic epithelium of the cervix. Arch Pathol Lab Med. 2019;143:279.
2. Hong SA, Yoo SH, Choi J, Robboy SJ, Kim K-R. A review and update on papillary immature metaplasia of the uterine cervix: a distinct subset of low-grade squamous intraepithelial lesion, proposing a possible cell of origin. Arch Pathol Lab Med. 2018;142:973–81.
3. Walts AE, Bose S. P16/Ki-67 immunostaining is useful in stratification of atypical metaplastic epithelium of the cervix. Clin Med Pathol. 2008;1:35–42.
4. Duggan MA, Akbari M, Magliocco AM. Atypical immature cervical metaplasia: immunoprofiling and longitudinal outcome. Hum Pathol. 2006;37:1473–81.
5. Iaconis L, Hyjek E, Ellenson LH, Pirog EC. p16 and Ki-67 immunostaining in atypical immature squamous metaplasia of the uterine cervix: correlation with human papillomavirus detection. Arch Pathol Lab Med. 2007;131:1343–9.
6. Trivijitsilp P, Mosher R, Sheets EE, Sun D, Crum CP. Papillary immature metaplasia (immature condyloma) of the cervix: a clinicopathologic analysis and comparison with papillary squamous carcinoma. Hum Pathol. 1998;29:641–8.
7. Weir MM, Bell DA, Young RH. Transitional cell metaplasia of the uterine cervix and vagina: an underrecognized lesion that may be confused with high-grade dysplasia. A report of 59 cases. Am J Surg Pathol. 1997;21:510–7.
8. Egan AJ, Russell P. Transitional (urothelial) cell metaplasia of the uterine cervix: morphological assessment of 31 cases. Int J Gynecol Pathol. 1997;16:89–98.
9. Murali R, Loughman NT, Pagliuso J, McKenzie PR, Watson GF, Earls P, et al. Cytological features of transitional cell metaplasia of the lower female genital tract. Pathology. 2010;42:113–8.
10. Harnden P, Kennedy W, Andrew AC, Southgate J. Immunophenotype of transitional metaplasia of the uterine cervix. Int J Gynecol Pathol. 1999;18:125–9.
11. Ismail SM. Cone biopsy causes cervical endometriosis and tubo-endometrioid metaplasia. Histopathology. 1991;18:107–14.
12. Oliva E, Clement PB, Young RH. Tubal and tubo-endometrioid metaplasia of the uterine cervix: unemphasized features that may cause problems in differential diagnosis: a report of 25 cases. Am J Clin Pathol. 1995;103:618–23.
13. Cameron RI, Maxwell P, Jenkins D, McCluggage WG. Immunohistochemical staining with MIB1, bcl2 and p16 assists in the distinction of cervical glandular intraepithelial neoplasia from tubo-endometrial metaplasia, endometriosis and microglandular hyperplasia. Histopathology. 2002;41:313–21.
14. Baker PM, Clement PB, Bell DA, Young RH. Superficial endometriosis of the uterine cervix: a report of 20 cases of a process that may be confused with endocervical glandular dysplasia or adenocarcinoma in situ. Int J Gynecol Pathol. 1999;18:198–205.
15. Nicolae A, Goyenaga P, McCluggage WG, Preda O, Nogales FF. Endometrial intestinal metaplasia: a report of two cases, including one associated with cervical intestinal and pyloric metaplasia. Int J Gynecol Pathol. 2011;30:492–6.
16. Mikami Y. Gastric-type mucinous carcinoma of the cervix and its precursors – historical overview. Histopathology. 2020;76:102–11.
17. Jones MA, Young RH. Atypical oxyphilic metaplasia of the endocervical epithelium: a report of six cases. Int J Gynecol Pathol. 1997;16:99–102.
18. Trowell JE. Intestinal metaplasia with argentaffin cells in the uterine cervix. Histopathology. 1985;9:551–9.
19. Sivridis E, Karpathiou G, Malamou-Mitsi V, Giatromanolaki A. Intestinal-type metaplasia in the original squamous epithelium of the cervix. Eur J Gynaecol Oncol. 2010;31:319–22.
20. Nucci MR, Ferry JA, Young RH. Ectopic prostatic tissue in the uterine cervix: a report of four cases and review of ectopic prostatic tissue. Am J Surg Pathol. 2000;24:1224–30.
21. Kelly P, McBride HA, Kennedy K, Connolly LE, McCluggage WG. Misplaced Skene's glands: Glandular elements in the lower female genital tract that are variably immunoreactive with prostate markers and that encompass vaginal tubulosquamous polyp and cervical ectopic prostatic tissue. Int J Gynecol Pathol. 2011;30:605–12.
22. McCluggage WG, Ganesan R, Hirschowitz L, Miller K, Rollason TP. Ectopic prostatic tissue in the uterine cervix and vagina: report of a series with a detailed immunohistochemical analysis. Am J Surg Pathol. 2006;30:209–15.
23. Roma AA. Sebaceous glands in the uterine cervix and vaginal wall: congenital misplacement, metaplastic process, or both? Int J Gynecol Pathol. 2010;29:488–9.
24. Rosa M, Moore G. Epidermalization of cervix and vagina: an unsolved dilemma. J Low Genit Tract Dis. 2008;12:217–9.
25. Szumiło J, Patel A, Patel S, Burdan F. Sebaceous glands: unusual histological finding in the uterine cervix. Folia Morphol (Warsz). 2009;68:287–9.
26. Kazakov DV, Hejda V, Kacerovska D, Michal M. Hyperplasia of ectopic sebaceous glands in the uterine cervix: case report. Int J Gynecol Pathol. 2010;29:605–8.
27. Alsaqobi A, Al-Brahim N. Osseous metaplasia of the cervix: a rare transformation can mimic a tumor. Literature review. Case Rep Pathol. 2018;2018:1392975.
28. Giannella L, Gelli MC, Mfuta K, Prandi S. A postconization hematometra revealed a rare case of endocervical bone metaplasia. J Low Genit Tract Dis. 2014;18:E19–22.
29. Elkattan E, Abdelbadei M, Abdelmoaty H, Ali E, Samir D, Kheidr H. Osseous metaplasia of the cervix: a rare transformation. J Turk Ger Gynecol Assoc. 2015;16:58–9.
30. Bedaiwy MA, Goldberg JM, Biscotti CV. Recurrent osseous metaplasia of the cervix after loop electrosurgical excision. Obstet Gynecol. 2001;98:968–70.
31. Sabatini L, Rainey AJ, Tenuwara W, Webb JB. Osseous metaplasia of cervical epithelium. BJOG. 2001;108:333–4.
32. Siddon A, Hui P. Glial heterotopia of the uterine cervix: DNA genotyping confirmation of its fetal origin. Int J Gynecol Pathol. 2010;29:394–7.
33. Doldan A, Otis CN, Pantanowitz L. Adipose tissue: a normal constituent of the uterine cervical stroma. Int J Gynecol Pathol. 2009;28:396–400.
34. Nucci MR. Pseudoneoplastic glandular lesions of the uterine cervix: a selective review. Int J Gynecol Pathol. 2014;33:330–8.
35. Roh MH, Agoston E, Birch C, Crum CP. P16 immunostaining patterns in microglandular hyperplasia of the cervix and their significance. Int J Gynecol Pathol. 2009;28:107–13.
36. Previs RA, Edwards JM, Secord AA, Nucci MR, Bentley RC, Hall AHS. Cystic fibrosis involving the cervix, mimicking a well-differentiated adenocarcinoma: a case report. Int J Gynecol Pathol. 2014;33:100–4.
37. Young RH, Scully RE. Atypical forms of microglandular hyperplasia of the cervix simulating carcinoma. A report of five cases and review of the literature. Am J Surg Pathol. 1989;13:50–6.
38. Young RH, Clement PB. Pseudoneoplastic glandular lesions of the uterine cervix. Semin Diagn Pathol. 1991;8:234–49.
39. Loureiro J, Oliva E. The spectrum of cervical glandular neoplasia and issues in differential diagnosis. Arch Pathol Lab Med. 2014;138:453–83.
40. Qiu W, Mittal K. Comparison of morphologic and immunohistochemical features of cervical microglandular hyperplasia with low-grade mucinous adenocarcinoma of the endometrium. Int J Gynecol Pathol. 2003;22:261–5.

41. Nucci MR, Clement PB, Young RH. Lobular endocervical glandular hyperplasia, not otherwise specified: a clinicopathologic analysis of thirteen cases of a distinctive pseudoneoplastic lesion and comparison with fourteen cases of adenoma malignum. Am J Surg Pathol. 1999;23:886–91.
42. Mikami Y, Hata S, Fujiwara K, Imajo Y, Kohno I, Manabe T. Florid endocervical glandular hyperplasia with intestinal and pyloric gland metaplasia: worrisome benign mimic of "adenoma malignum". Gynecol Oncol. 1999;74:504–11.
43. Kato N, Sugawara M, Maeda K, Hosoya N, Motoyama T. Pyloric gland metaplasia/differentiation in multiple organ systems in a patient with Peutz-Jegher's syndrome. Pathol Int. 2011;61:369–72.
44. Talia KL, McCluggage WG. The developing spectrum of gastric-type cervical glandular lesions. Pathology. 2018;50:122–33.
45. Matsubara A, Sekine S, Ogawa R, Yoshida M, Kasamatsu T, Tsuda H, et al. Lobular endocervical glandular hyperplasia is a neoplastic entity with frequent activating GNAS mutations. Am J Surg Pathol. 2014;38:370–6.
46. Jones MA, Young RH, Scully RE. Diffuse laminar endocervical glandular hyperplasia. A benign lesion often confused with adenoma malignum (minimal deviation adenocarcinoma). Am J Surg Pathol. 1991;15:1123–9.
47. Fluhmann CF. Focal hyperplasis (tunnel clusters) of the cervix uteri. Obstet Gynecol. 1961;17:206–14.
48. Segal GH, Hart WR. Cystic endocervical tunnel clusters. A clinicopathologic study of 29 cases of so-called adenomatous hyperplasia. Am J Surg Pathol. 1990;14:895–903.
49. Rabban JT, McAlhany S, Lerwill MF, Grenert JP, Zaloudek CJ. PAX2 distinguishes benign mesonephric and mullerian glandular lesions of the cervix from endocervical adenocarcinoma, including minimal deviation adenocarcinoma. Am J Surg Pathol. 2010;34:137–46.
50. Daya D, Young RH. Florid deep glands of the uterine cervix. Another mimic of adenoma malignum. Am J Clin Pathol. 1995;103:614–7.
51. Clement PB, Young RH. Deep nabothian cysts of the uterine cervix. A possible source of confusion with minimal-deviation adenocarcinoma (adenoma malignum). Int J Gynecol Pathol. 1989;8:340–8.
52. Young RH, Clement PB. Endocervicosis involving the uterine cervix: a report of four cases of a benign process that may be confused with deeply invasive endocervical adenocarcinoma. Int J Gynecol Pathol. 2000;19:322–8.
53. Mirkovic J, Schoolmeester JK, Campbell F, Miron A, Nucci MR, Howitt BE. Cervical mesonephric hyperplasia lacks *KRAS*/*NRAS* mutations. Histopathology. 2017;71:1003–5.
54. Jones MA, Andrews J, Tarraza HM. Mesonephric remnant hyperplasia of the cervix: a clinicopathologic analysis of 14 cases. Gynecol Oncol. 1993;49:41–7.
55. Howitt BE, Nucci MR. Mesonephric proliferations of the female genital tract. Pathology. 2018;50:141–50.
56. Seidman JD, Tavassoli FA. Mesonephric hyperplasia of the uterine cervix: a clinicopathologic study of 51 cases. Int J Gynecol Pathol. 1995;14:293–9.
57. Ferry JA, Scully RE. Mesonephric remnants, hyperplasia, and neoplasia in the uterine cervix. A study of 49 cases. Am J Surg Pathol. 1990;14:1100–11.
58. Pors J, Cheng A, Leo JM, Kinloch MA, Gilks B, Hoang L. A comparison of GATA3, TTF1, CD10, and calretinin in identifying mesonephric and mesonephric-like carcinomas of the gynecologic tract. Am J Surg Pathol. 2018;42:1596–606.
59. Roma AA, Goyal A, Yang B. Differential expression patterns of GATA3 in uterine mesonephric and nonmesonephric lesions. Int J Gynecol Pathol. 2015;34:480–6.
60. Howitt BE, Emori MM, Drapkin R, Gaspar C, Barletta JA, Nucci MR, et al. GATA3 is a sensitive and specific marker of benign and malignant mesonephric lesions in the lower female genital tract. Am J Surg Pathol. 2015;39:1411–9.
61. Kenny SL, McBride HA, Jamison J, McCluggage WG. Mesonephric adenocarcinomas of the uterine cervix and corpus: HPV-negative neoplasms that are commonly PAX8, CA125, and HMGA2 positive and that may be immunoreactive with TTF1 and hepatocyte nuclear factor 1-β. Am J Surg Pathol. 2012;36:799–807.
62. Casey S, McCluggage WG. Adenomyomas of the uterine cervix: report of a cohort including endocervical and novel variants [corrected]. Histopathology. 2015;66:420–9.
63. Clement PB, Young RH, Keh P, Ostör AG, Scully RE. Malignant mesonephric neoplasms of the uterine cervix. A report of eight cases, including four with a malignant spindle cell component. Am J Surg Pathol. 1995;19:1158–71.
64. Tambouret R, Clement PB, Young RH. Endometrial endometrioid adenocarcinoma with a deceptive pattern of spread to the uterine cervix: a manifestation of stage IIb endometrial carcinoma liable to be misinterpreted as an independent carcinoma or a benign lesion. Am J Surg Pathol. 2003;27:1080–8.
65. Jayakumar NK. Cervicitis: How often is it non-specific! J Clin Diagn Res. 2015;9(3):EC11–2.
66. Young RH, Harris NL, Scully RE. Lymphoma-like lesions of the lower female genital tract: a report of 16 cases. Int J Gynecol Pathol. 1985;4:289–99.
67. Singh A, Vats G, Radhika AG, Meena P, Radhakrisnan G. Cervical xanthogranuloma in a case of postmenopausal pyometra. Obstet Gynecol Sci. 2016;59:411–4.
68. Ramdial PK, Sing Y, Chotey NA, Bagratee JS. Concomitant malacoplakia and granuloma inguinale of the cervix in acquired immune deficiency syndrome. Int J Gynecol Pathol. 2008;27:282–7.
69. Stewart CJ, Thomas MA. Malacoplakia of the uterine cervix and endometrium. Cytopathology. 1991;2:271–5.
70. Baithun M, Freeman-Wang T, Chowdary P, Kadir RA. Ligneous cervicitis and endometritis: a gynaecological presentation of congenital plasminogen deficiency. Haemophilia. 2018;24:359–65.
71. Taube ET, Frangini S, Caselitz J, Chiantera V, Pahl S, Vercellino GF, et al. Ligneous cervicitis in a woman with plasminogen deficiency associated with an atypical form of microglandular hyperplasia: a case report and review of literature. Int J Gynecol Pathol. 2013;32:329–34.
72. Ganesan R, Ferryman SR, Meier L, Rollason TP. Vasculitis of the female genital tract with clinicopathologic correlation: a study of 46 cases with follow-up. Int J Gynecol Pathol. 2000;19:258–65.
73. Roma AA, Amador-Ortiz C, Liapis H. Significance of isolated vasculitis in the gynecological tract: what clinicians do with the pathologic diagnosis of vasculitis? Ann Diagn Pathol. 2014;18:199–202.
74. Hernández-Rodríguez J, Tan CD, Rodríguez ER, Hoffman GS. Gynecologic vasculitis: an analysis of 163 patients. Medicine (Baltimore). 2009;88:169–81.
75. Cheung VYT, Ma PWS. Cervical ulcer in Behçet's disease. J Obstet Gynaecol Can. 2011;33:201.
76. Paavonen J, Vesterinen E, Meyer B, Saksela E. Colposcopic and histologic findings in cervical chlamydial infection. Obstet Gynecol. 1982;59:712–5.
77. Agarwal J, Gupta JK. Female genital tuberculosis – a retrospective clinico-pathologic study of 501 cases. Indian J Pathol Microbiol. 1993;36:389–97.
78. McGalie CE, McBride HA, McCluggage WG. Cytomegalovirus infection of the cervix: morphological observations in five cases of a possibly under-recognised condition. J Clin Pathol. 2004;57:691–4.
79. Andrianjafitrimo HT, Ranaivomanana VF, Ravelomampitoniainarivony TM, Ramiandrasoa LA, Randrianjafisamindrakotroka NS. Schistosomiasis of the female genital tract: a two-center study. Med Sante Trop. 2019;29:306–9.
80. Helling-Giese G, Sjaastad A, Poggensee G, Kjetland EF, Richter J, Chitsulo L, et al. Female genital schistosomiasis (FGS): relationship between gynecological and histopathological findings. Acta Trop. 1996;62:257–67.

81. Schneider V. Arias-Stella reaction of the endocervix: frequency and location. Acta Cytol. 1981;25:224–8.
82. Nucci MR, Young RH. Arias-Stella reaction of the endocervix: a report of 18 cases with emphasis on its varied histology and differential diagnosis. Am J Surg Pathol. 2004;28:608–12.
83. Arias-Stella J. The Arias-Stella reaction: facts and fancies four decades after. Adv Anat Pathol. 2002;9:12–23.
84. Ip PPC, Wang S-Y, Wong OGW, Chow K-L, Lee HH-Y, Cheung ANY, et al. Napsin A, hepatocyte nuclear factor-1-beta (HNF-1β), estrogen and progesterone receptors expression in Arias-Stella reaction. Am J Surg Pathol. 2019;43:325–33.
85. Vang R, Barner R, Wheeler DT, Strauss BL. Immunohistochemical staining for Ki-67 and p53 helps distinguish endometrial Arias-Stella reaction from high-grade carcinoma, including clear cell carcinoma. Int J Gynecol Pathol. 2004;23:223–33.
86. Ji JX, Cochrane DR, Tessier-Cloutier B, Leung S, Cheng AS, Chow C, et al. Use of immunohistochemical markers (HNF-1β, Napsin A, ER, CTH, and ASS1) to distinguish endometrial clear cell carcinoma from its morphologic mimics including Arias-Stella reaction. Int J Gynecol Pathol. 2019. https://doi.org/10.1097/PGP.0000000000000609int.
87. Yelverton CL, Bentley RC, Olenick S, Krigman HR, Johnston WW, Robboy SJ. Epithelial repair of the uterine cervix: assessment of morphologic features and correlations with cytologic diagnosis. Int J Gynecol Pathol. 1996;15:338–44.
88. Val-Bernal JF, Pinto J, Garijo MF, Gómez MS. Pagetoid dyskeratosis of the cervix: an incidental histologic finding in uterine prolapse. Am J Surg Pathol. 2000;24:1518–23.
89. Boyle DP, McCluggage WG. Pseudoinvasion of benign squamous epithelium following cervical biopsy: a pseudoneoplastic phenomenon mimicking invasive squamous carcinoma. J Clin Pathol. 2011;64:1093–6.
90. Lesack D, Wahab I, Gilks CB. Radiation-induced atypia of endocervical epithelium: a histological, immunohistochemical and cytometric study. Int J Gynecol Pathol. 1996;15:242–7.