



# Introduction: general principles in the evaluation of endometrial samples

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## Introduction

An algorithmic approach to the endometrial biopsy is presented in this book, which in most instances requires evaluation of the entire sample at low magnification and then at increasingly higher magnifications. Although we feel this approach more user friendly, inherent subjectivity in the examination of a sample makes this a little more difficult. Nowhere is this subjectivity more pronounced than in the evaluation of hyperplasia of the endometrium, where interobserver variability for a variety of parameters is less than ideal. Therefore, entities may feature in more than one section, and are cross-referenced between chapters, with a more detailed description in the chapter where the lesion most commonly fits.

Endometrial samples are among the most common specimens evaluated by the surgical pathologist and some of the most vexing. The difficulty in the evaluation of the endometrial sample lies, at least in part, in the variability of morphologic patterns seen in the normal endometrium, which undergoes cyclic changes in response to hormonal stimuli. The lack of orientation of the specimen, the frequent contamination of elements from the lower genital tract, and fragmentation further complicate evaluation of the specimen. As with all other surgical specimens, a pertinent clinical history eases the pathologist's job, but is rarely adequately supplied. However, this should not dissuade the pathologist from seeking this information, as it often makes the interpretation of a sample easier. Age and hormone use are the two most pertinent components of history when evaluating an endometrial sample. Abnormal uterine bleeding is the most frequent driver for endometrial sampling, and the reasons for abnormal uterine bleeding are somewhat different in the different age groups, with pregnancy-related causes predominating in the

reproductive age group, and atrophy and neoplasia predominating in the postmenopausal age group. However, the pathologist should remember that there is wide variation in the age of menopause amongst different populations, and it would be imprudent to assume that a 55-year-old woman is necessarily postmenopausal. Hormonal manipulation is commonly used to manage abnormal uterine bleeding and, as expected, can alter the appearance of the endometrium to a remarkable extent. Progesterone use, in particular, can mask atypia in the endometrium and is an extremely important component of endometrial assessment in a patient with a prior history of endometrial precancer or cancer.

Endometrial sampling may be performed for a variety of indications. Sampling in a patient with abnormal uterine bleeding is done to identify an organic cause of uterine bleeding (e.g., polyp or submucous leiomyoma) and to exclude a neoplastic condition (e.g., hyperplasia or carcinoma). Although hormonal dysregulation is the most common cause of abnormal uterine bleeding, pathologic assessment of the hormonal milieu of the endometrium rarely contributes to the management of the patient. Nevertheless, erroneously ascribing an organic cause to a bleeding that actually has a hormonal basis may unnecessarily complicate the patient's management. Another common endometrial sample is one received in association with loss of pregnancy. Evaluation of the endometrial sample for endometrial dating in the management of infertility is distinctly uncommon these days, especially as recent studies have demonstrated sufficient interobserver variability in the assessment of features necessary to accurately diagnose luteal phase defect (1). On the other hand, endometrial biopsies are increasingly performed to screen for endometrial neoplasia in patients at risk for development of endometrial carcinoma (patients on tamoxifen therapy or in patients with Lynch syndrome) (2).

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An endometrial sample may be obtained through a biopsy or an endometrial curettage. Typically, the former is a procedure done in the office without anesthesia, and the latter is a procedure performed under general anesthesia. Aspiration biopsies, in particular, have gained favor in recent times. The endometrial biopsy has an inherent false-negative rate because the entire endometrium is not removed for evaluation (3). Therefore, while a positive result is highly accurate, a negative result is only moderately useful. The likelihood of a false-negative result may be higher in postmenopausal women and in women who have received progestin therapy (3,4). Accordingly, an endometrial curettage should follow in cases with a negative biopsy if the clinical picture is concerning for a more ominous diagnosis. A curettage, if performed well, provides more or less the entire endometrium for evaluation, although irregularities in the uterus may interfere with the ability to remove the endometrium in its entirety. In this book, we make no distinctions between biopsies or curettages unless specifically stated, and both are variably referred to as “samplings” or “biopsies.”

Grossing of endometrial samples

In general, in cases where sampling is performed for the evaluation of abnormal uterine bleeding, we recommend the submission of the entire sample for histologic evaluation with a few minor exceptions. We treat these samples as biopsies and examine three levels in each block, although if the tissue is voluminous (in excess of five blocks) a single level per block is examined. In cases where a loss of pregnancy has occurred, we recommend submission of two tissue blocks, although we make allowance for the submission of a single block in cases with voluntary interruption of pregnancy provided that an adequate sample of both the decidua and villous tissue is submitted for histologic evaluation. Although villous tissue has traditionally been prioritized in the evaluation of termination samples, evaluation of the decidua can reveal lesions that may impact subsequent pregnancies and possibly provide insight into the loss of pregnancy in cases with recurrent abortion. In addition, in the event that gestational trophoblastic disease is suspected, maternal tissues may be needed for comparative molecular analyses.

General microscopic evaluation of endometrial samples

As with all pathologic samples, the pathologist should review the sample at a low magnification and assess the following criteria:

- 1. Presence of extraneous tissues/foreign material
- 2. Adequacy of sample/volume of tissue
- 3. Uniformity of sample/presence of focal variations or presence of lesion
- 4. The ratio of glands to stroma in various areas
- 5. Glandular morphology and cytology
- 6. Stromal morphology and alterations.

A general overview of this pattern-based evaluation is provided in the remainder of this chapter, with more detailed assessment in the following chapters.

Extraneous elements/artifacts in an endometrial sample

The pathologist should be familiar with tissues that are extraneous to the endometrium, as well as common artifacts that can confuse the interpretation of an endometrial sample.

Artifacts

Pseudolipomatous change is particularly common in an endometrial sample (5). Pseudolipomatosis (Fig. 1.1a) refers to the presence of vacuolated structures simulating fat in a tissue sample. It is hypothesized to be the result of admixture of tissues with air when a suction sample is obtained. It should not be confused with the presence of fat in an endometrial sample (Fig. 1.1b), which is invariably but not always an indication of uterine perforation, and considered a significant finding deserving of direct communication with the clinician (6).

Another change that is commonly seen in endometrial biopsies is stromal disruption leading to an artifactual impression of glandular crowding (Fig. 1.2). Therefore, evaluation of crowding must be performed in areas where the stroma is relatively intact. A similar “artificial crowding” happens when glands telescope within themselves (Fig. 1.2).

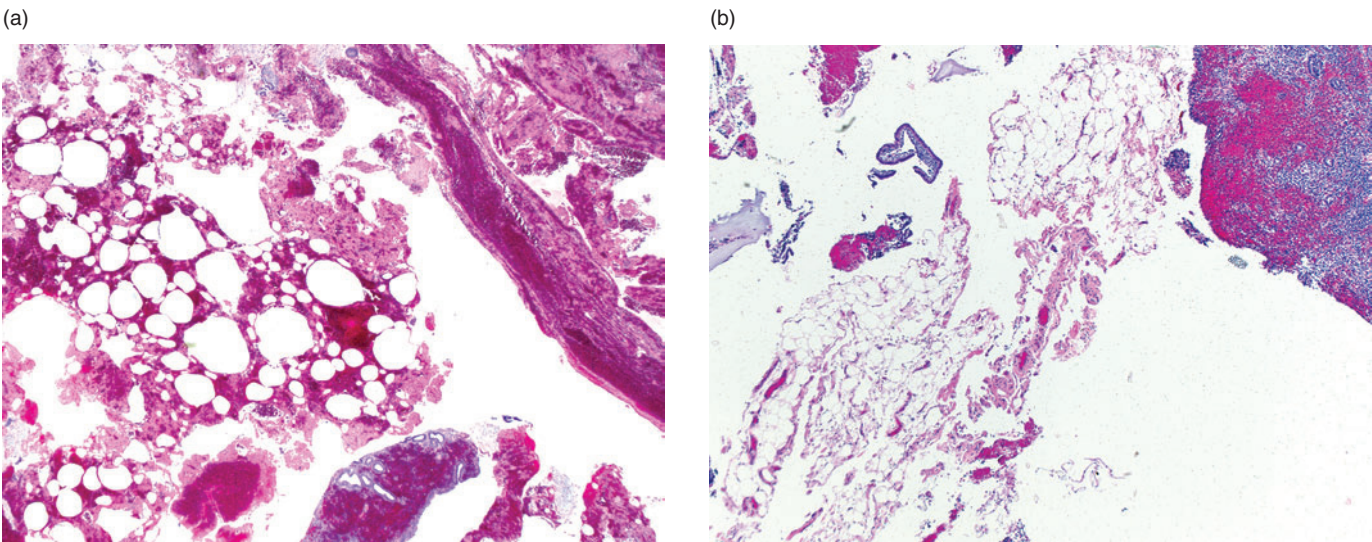
Extraneous tissue and contaminants

As endometrial tissues represent a jumbled mass of tissue fragments, determining that a tissue fragment is truly a floater is harder than usual, and the pathologist should always be alert to this possibility.

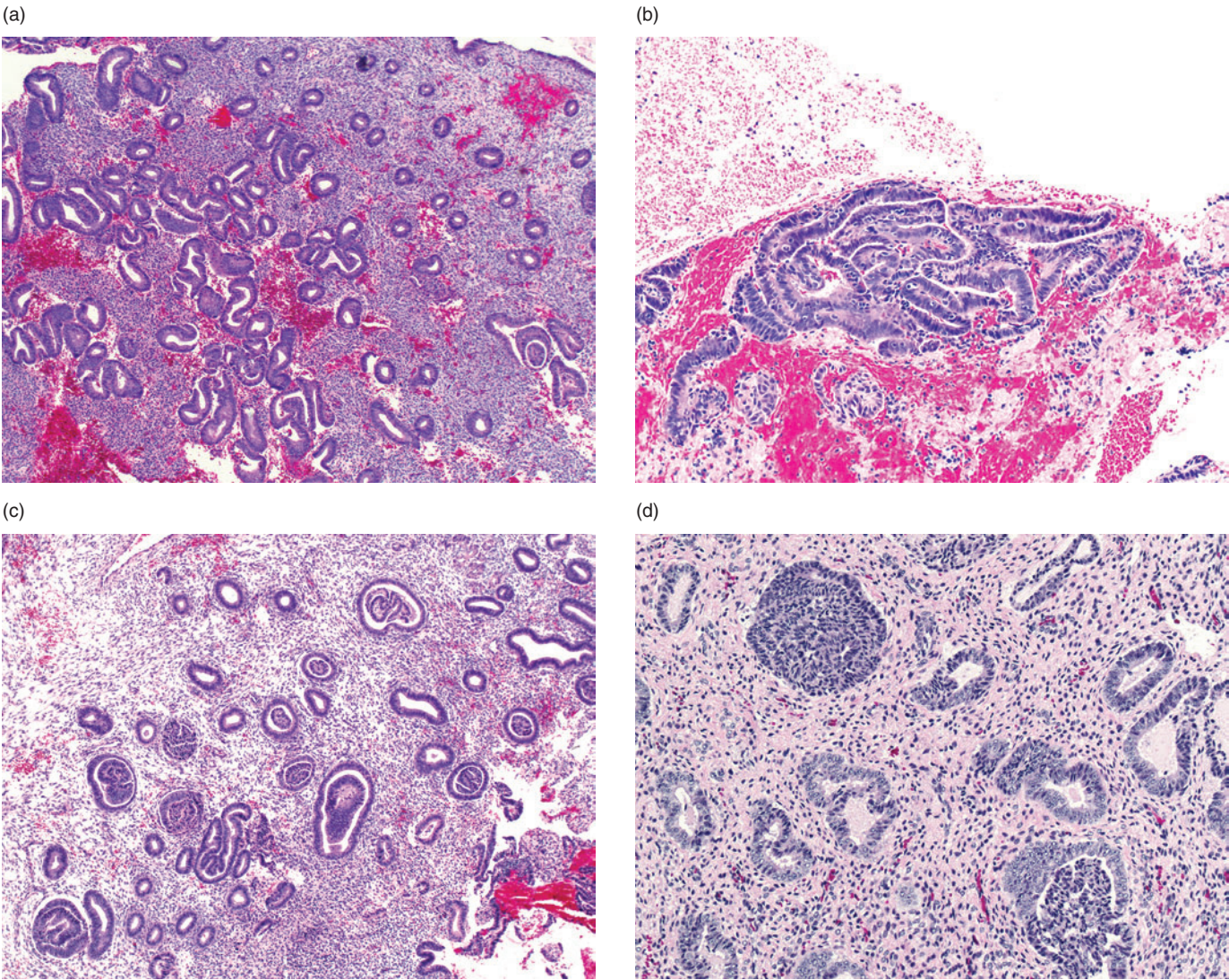
Tissues from the lower genital tract are common contaminants of an endometrial sample, and include squamous epithelium and endocervical tissues. In particular, it is common to see the cervical mucus plug with its acute inflammatory exudate admixed with an endometrial sample, and this should not be misconstrued as evidence of acute endometritis. Likewise, a fragment of carcinoma in an endometrial curettage should not be assumed to arise from the endometrium, as it may originate from the endocervix. There is significant overlap in histology and immunohistochemistry between endometrial and endocervical carcinoma, and this distinction may be difficult even in hysterectomy specimens. Indeed, on occasion, cervical adenocarcinoma may colonize the endometrial cavity and simulate endometrial carcinoma even in the hysterectomy specimen (see additional discussion in section on carcinoma – Chapter 4, Fig. 4.6). Evaluation of the background endometrium and the stroma can assist in this evaluation. Contaminants from other tissue samples (“floaters”) are also more common considerations in the endometrial sample, because of the inherently fragmented nature of the sample. The use of molecular identity testing using short tandem repeats is useful in this circumstance, but should



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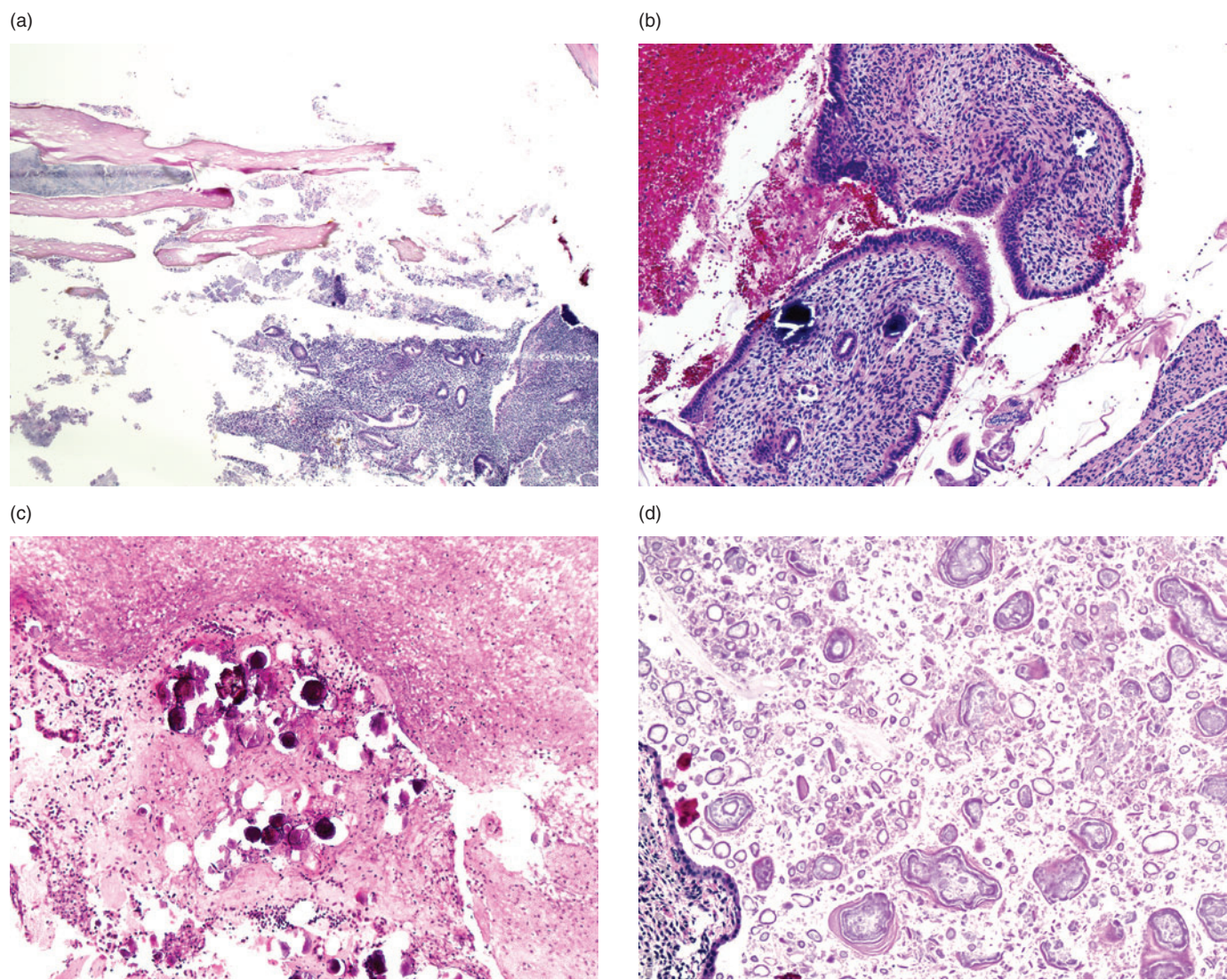
**Figure 1.1** (a) Endometrial biopsy with pseudolipomatous change. Note variably sized cleared spaces with intervening blood. Vessels and supporting structures that are characteristic of fat are not identified (b).



**Figure 1.2** (a) Artificial crowding in an endometrial sample. The stroma has fragmented, and the glands appear crowded. Comparison with well-preserved intact fragments is useful to make the distinction. (b) A stripped glandular fragment has folded over itself, giving the false impression of a complex glandular structure. (c) Telescoped endometrial glands. (d) Telescoped and distorted endometrial gland simulating morular metaplasia.



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**Figure 1.3** (a) Bony spicules in the endometrium of an elderly patient. (b) Psammoma bodies associated with benign endometrium in a patient on hormonal therapy. Neoplasia was not identified. (c) Numerous psammoma bodies in a curettage in a patient eventually found to have an adnexal mass with a borderline serous ovarian tumor. Epithelial elements are not readily evident; however, close inspection showed minute papillary epithelial clusters in other areas. (d) Liesegang rings in a distended endometrial gland, with superficial resemblance to psammoma bodies.

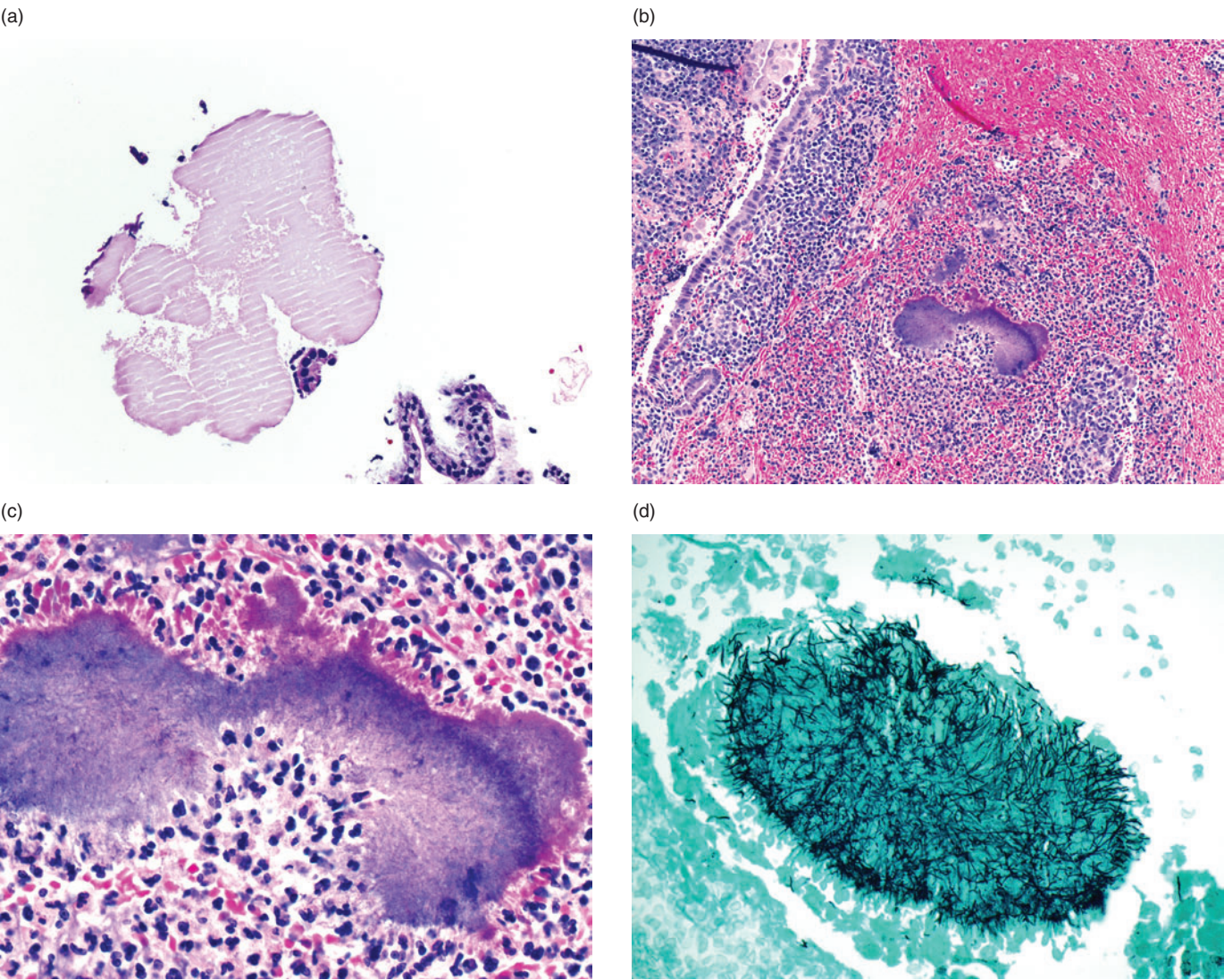
be interpreted with caution in endometrial neoplasia. Endometrial neoplasia is not uncommonly affected by microsatellite instability, and this can lead to an erroneous interpretation that the tissue is a contaminant when in reality the tissue belongs to the patient (7). A similar issue may arise in gestational samples, where the pregnancy was the result of a donor rather than the gestational mother (discussed in Chapter 8).

Adipose tissue (Fig. 1.1b) and rarely intestinal tissue indicate uterine perforation, although rarely adipose tissue may derive from a lipoma or lipoleiomyoma (6). Cartilage and bone (Fig. 1.3a) have occasionally been found in endometrial samples and can reflect a retained remote conceptus or metaplasia of the endometrium (8,9). Rare cases with stone formation (uterine lithiasis) have been reported in the endometrial cavity (10). Calcification and psammoma bodies (Fig. 1.3b,c) are

uncommonly found in endometrial samples. Although traditionally considered ominous, and worrisome for neoplasia of the uterus and upper genital tract (tubes, ovary, or peritoneum) (11), systematic analysis shows that these arise more commonly in association with benign lesions (12–14). They are more commonly seen in association with hormone therapy, endometrial polyps, and atrophy. The presence of additional clinical findings (e.g., adnexal masses) or pathology drives further management, with more detailed investigation directed to patients with adnexal lesions. Psammoma bodies should be distinguished from Liesegang rings (Fig. 1.3d), which appear as concentric lamellated structures, owing to ill-understood mechanisms of deposition of minerals (15). They tend to be associated with cystic structures, and we have seen them in cystic endometrial glands (Fig. 1.3), where the



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**Figure 1.4** A pseudactinomycotic radiate granule in an endometrial biopsy in a patient with IUD (a). True actinomycoses were not identified in this case. Actinomycoses shows a finely fibrillar radiate appearance (b, c) that stains with grocott (d) and bacterial stains. Note the associated endometritis.

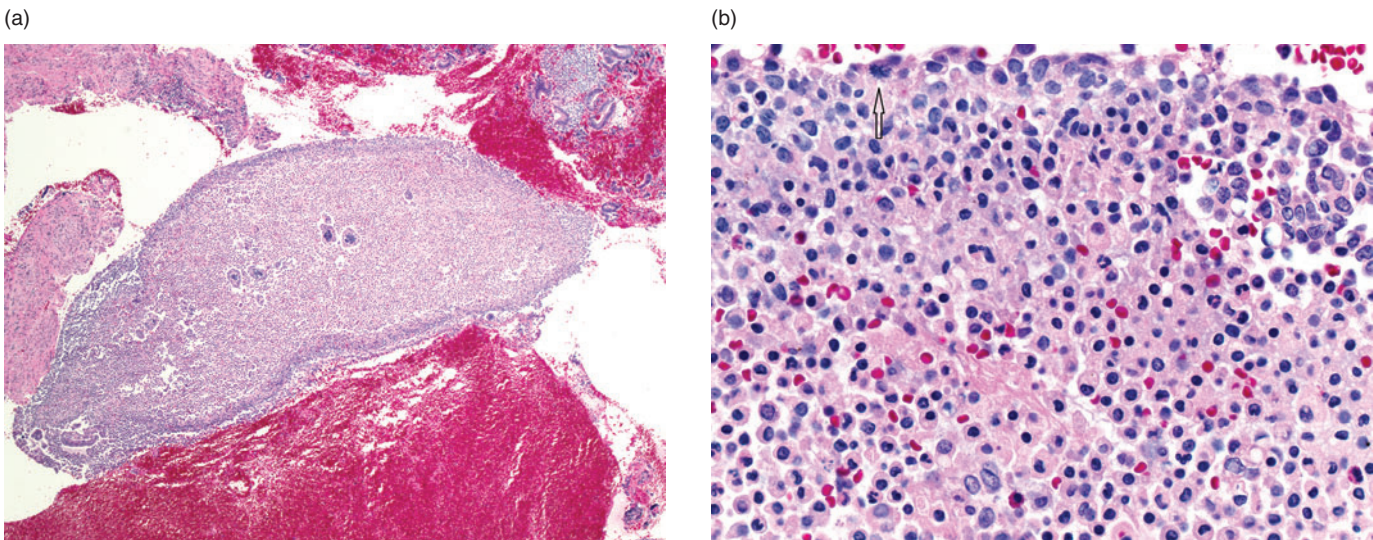
mechanism of formation likely duplicates that seen in endometriosis (15). Pseudoactinomycotic radiate granules (PAMRAGs) (Fig. 1.4a) are another structure that forms in the endometrial cavity, likely due to deposition and encrustation of material on a nidus of variable composition. PAMRAGs are often crystalline and refractile with broad peripheral clubs, while *Actinomyces* (Fig. 1.4b–d) show a dense eosinophilic center with slender peripheral filaments. Although a Gomori methenamine silver stain is negative in PAMRAGs (while being positive in *Actinomyces*), a Brown and Brenn stain will stain PAMRAGs; therefore, attention to the pattern of staining is essential. In *Actinomyces* the filaments are positive, whereas for PAMRAGs there is a strong diffuse staining pattern. These may coexist with true *Actinomyces*, from which they should be distinguished as the latter require antibiotic therapy. Both PAMRAGs and *Actinomyces* show an association with intra-uterine contraceptive device use (16).

Another finding that can be seen in endometrial tissues is that of collections of histiocytes (Fig. 1.5a,b). These differ from the foamy stromal histiocytes, described in the section on endometrial stroma. Luminal collections of histiocytes, when scant, rarely raise concern; however, when large aggregates form, sometimes with mitotic activity, they raise concern for neoplasia (17). Peculiar orientation on stromal fragments can simulate squamous- or clear-cell carcinoma. These are not of consequence and likely represent reactive changes to injury or foreign material. The significance of other histiocytic proliferations in endometrial samplings is discussed in Chapter 7.

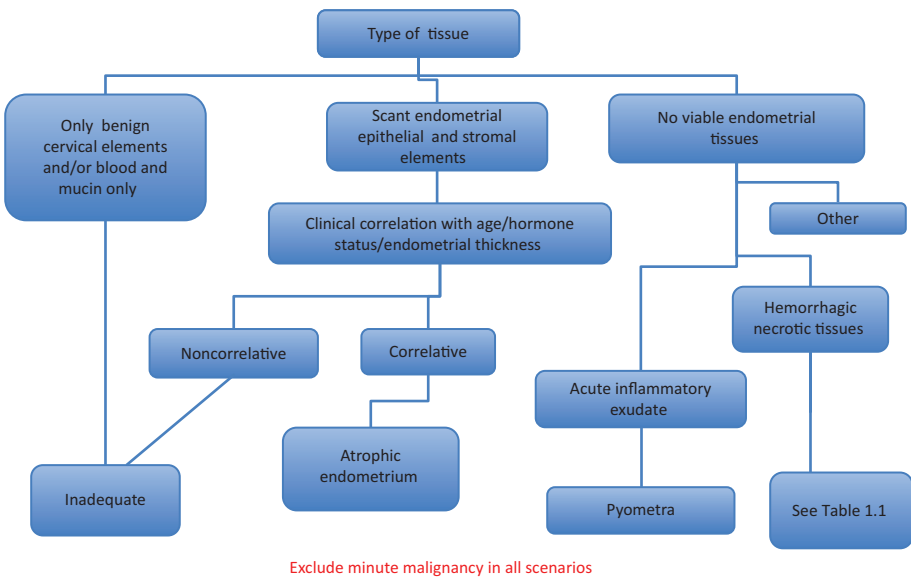
Rarely, refractile material, consistent with talc, suture material, or other foreign material may be present in an endometrial sample, presumably introduced during examination. A bright golden yellow pigment is occasionally seen in patients who have undergone endometrial ablation (18).



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**Figure 1.5** Large nodular histiocytic aggregate in an endometrial biopsy with peculiar organization and entrapped endometrial elements (a). Higher magnification shows characteristic monomorphic population of cells (b). Mitotic activity and atypia may be present. Immunohistochemical stains readily identify this as a histiocytic proliferation.



**Flow chart 1.1** Overview of assessment of a potentially inadequate endometrial sample.

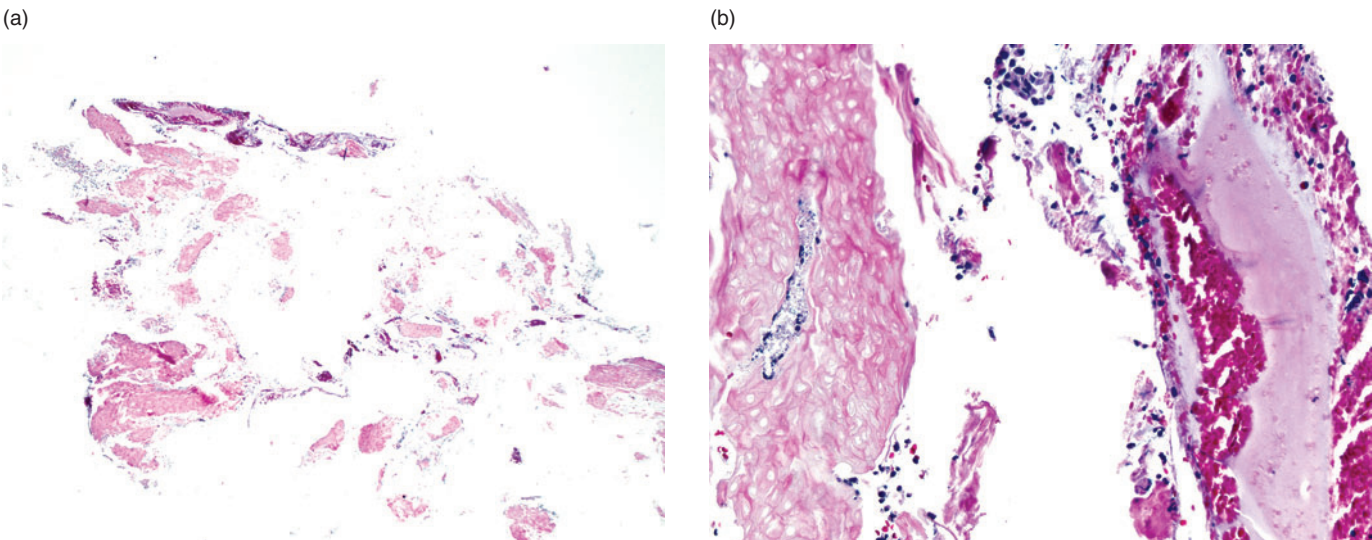
Exclude minute malignancy in all scenarios

Adequacy of an endometrial sample

The labeling of a sample as inadequate rests on the reasons why the sample is considered inadequate (Flow chart 1.1). In our opinion, simply to report the sample as inadequate or insufficient is, well, inadequate. A truly uninformative sample is one where there is no endometrial tissue in the sample and no information can be gleaned from said sample, therefore requiring repeat sampling. Often, the clinician is expecting such a result, because they had a failed attempt at an office endometrial sampling but decided to send whatever minimal sample was obtained for a pathologic evaluation. The specimen is

often scant and composed of wispy mucin and inflammatory cells, with some cervical elements. A sample may show scant amounts of viable endometrial elements, but may still give sufficient clues to direct further management or suggest underlying pathology, and it would be inappropriate to label such a sample as inadequate, akin to a pap smear sample that does not meet the cellular volume for adequacy but still has atypical cells. Even a near-acellular specimen can have informative elements (Fig. 1.6). In particular, samples that appear to be only blood clot should be evaluated with caution. Necrotic tissue tends to be admixed with a large volume of blood and may be indicative of an underlying malignancy,

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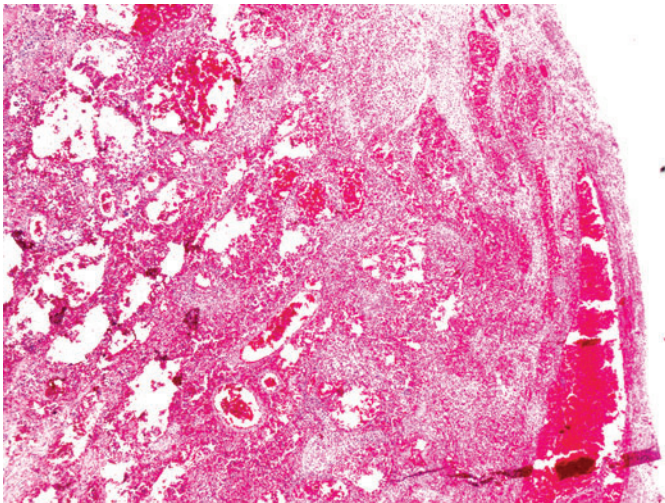
**Figure 1.6** An apparently insufficient endometrial sample composed of acellular fragments of mucus and squamous material (a). This amount of acellular squamous material is unlikely to be contaminant from a benign lesion of the cervix. In addition, the “ghost-like” squamous material is not typical of that seen with hyperkeratotic lesions of the cervix, which tends to have compact hyperkeratosis (b). The clinical setting of a postmenopausal woman is also atypical for a hyperkeratotic cervical lesion. A repeat sampling was requested, which revealed an endometrial carcinoma with extensive squamous metaplasia.

**Table 1.1** Necrotic hemorrhagic tissues in endometrial samples.

- Pseudodecidual cast from progestin therapy
- Necrotic decidua in a patient with complete spontaneous loss of pregnancy
- Infarcted endometrial polyp
- Infarcted leiomyoma
- Infarcted/necrotic malignancy, especially adenosarcoma, leiomyosarcoma, and malignant mixed Müllerian tumors

especially in a postmenopausal woman. Lesions that tend to present as necrotic specimens include prolapsed, strangulated, and infarcted polypoid lesions such as endometrial polyps and leiomyoma (Table 1.1). In addition, progestin-treated endometria shed as “casts” with ghosts of the underlying structure barely evident. These can mistakenly suggest an underlying neoplastic process (Fig. 1.7). Therefore, correlation with age and clinical history is important to advise the clinician on further evaluation.

Pathologists vary widely in their assessment of an endometrial sample as inadequate; as many as 30% of pipelle samples are reported as inadequate by pathologists (19). Likewise, gynecologists vary equally widely in their follow-up to a pathology report indicating an inadequate endometrial sample, and at least some follow up with a formal curettage. However, studies indicate that significant pathology is rarely missed when a small sample is procured in the clinical setting of atrophy, where endometrial thickness is established as less than 5 mm on hysteroscopy or ultrasound (20). In this setting, as long as the endometrial fragments themselves are atrophic/inactive, we report these samples as “atrophic endometrium,” and comment in a note that the findings are consistent with hysteroscopic/sonographic findings. On the other hand, if

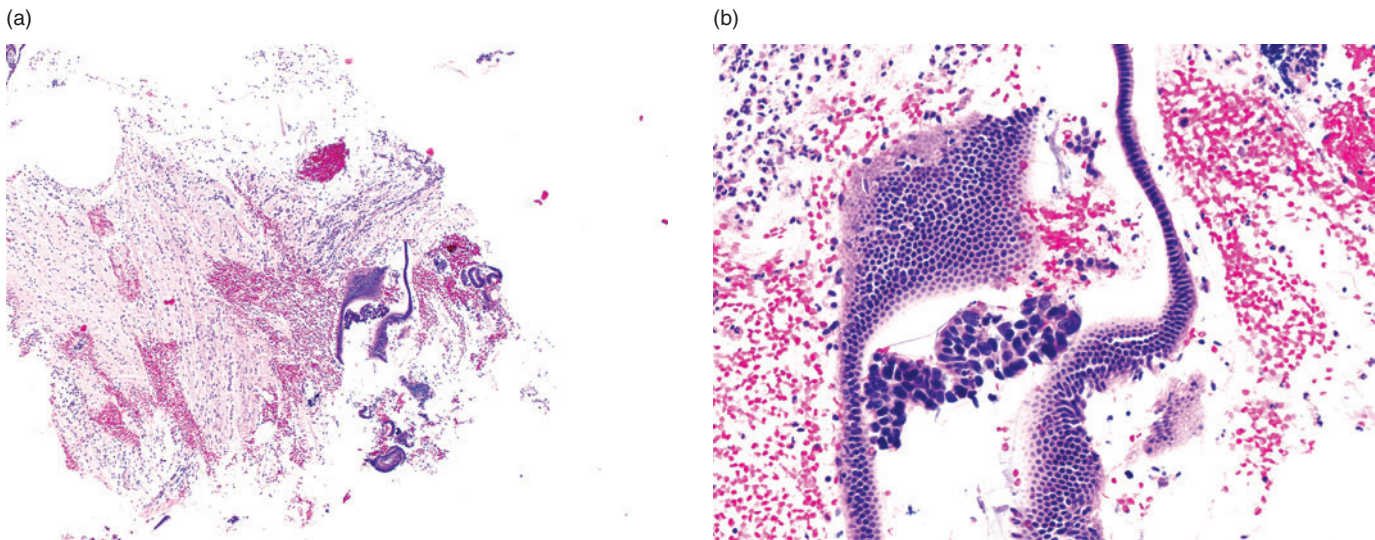


**Figure 1.7** An apparent bloody sample. However, an underlying architecture of vessels is appreciable, as are ghosts of glands. This is an endometrial cast, shed by a patient with a history of hyperplasia and progestin therapy. The patient continued to bleed in spite of the institution of progestins.

endometrial tissue is scant, when clinical findings indicate that a larger volume of tissue should have been retrieved we report the sample as “insufficient or inadequate,” with a comment indicating the noncorrelation with clinical findings and a suggestion, if pertinent, for additional sampling and follow-up. Care should be taken in examining even an atrophic sample to exclude scant fragments of carcinoma. Atrophic endometrium is nonstratified, with flattened-to-cuboidal cells, with an absence of mitotic activity. Such samples should be examined closely, especially as Type II endometrial carcinoma arises in an atrophic background and minute fragments of carcinoma may be admixed with atrophic endometrium (Fig. 1.8). In



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**Figure 1.8** Scant sample, composed largely of mucin and inflammatory cells with scant stripped atrophic glandular epithelium (a). However, between two fragments of atrophic epithelium is a fragment with features of malignancy with obvious hyperchromasia and marked atypia (b). A subsequent hysterectomy revealed a serous endometrial carcinoma.

addition, minute fragments of carcinoma may shed in an atrophic endometrial sample in cases where tubo-ovarian/peritoneal carcinoma is eventually diagnosed (21). Correlation with a concurrent cervicovaginal cytology, if available, is often useful in these cases. Unfortunately, in some cases, a mass is often not present on clinical evaluation, and there could be a delay in treatment if consideration is not given to the possibility of an occult tubo-ovarian or peritoneal primary.

Uniformity of sample and focal variations

A minor level of variability in an endometrial sample (e.g., occasional presence of subnuclear vacuoles in rare glands, presence of luminal secretions, foci of crowded glands) is the rule, especially in secretory endometrium, and undue significance should not be placed on minor variability in different fragments within an endometrial biopsy. Larger fragments of endometrium showing patterns distinct from the remainder of the endometrium are of significance, with two exceptions. The lower uterine segment appears different from the cycling endometrium, being less responsive to hormones than the functionalis. Likewise, the basalis endometrium is also different from the functionalis, and the pathologist should be alert to these possibilities and not diagnose focal lesions based only on the fibrotic nature of the stroma.

Ratio of glands to stroma

The ratio of glands to stroma in the endometrium should be assessed overall, but also in individual fragments. As expected, glandular neoplasia results in an excess of glands, whereas stromal neoplasia results in an expansion of that compartment. When assessing the gland-to-stroma ratio, the area of the

lumen of the gland is included in the “glandular component” (see also Chapter 3). The normal ratio of glands to stroma in a proliferative endometrium is 1:1 or less. There is an apparent increase in the glandular element as the proliferative cycle progresses and glands begin to coil, such that the normal ratio of glands to stroma in early secretory endometrium may be slightly in excess of 1:1 (Fig. 1.9). In late secretory endometrium, the gland-to-stroma ratio decreases again, as the stromal compartment expands due to predecidualization. Artifactual excess of glandular tissue may be seen in cases with stromal dissolution, or if the epithelium is stripped off the stroma and coiled on itself (Fig. 1.2b). Evaluation of an endometrial sample along these lines typically results in the following scenarios, which are addressed in the subsequent chapters:

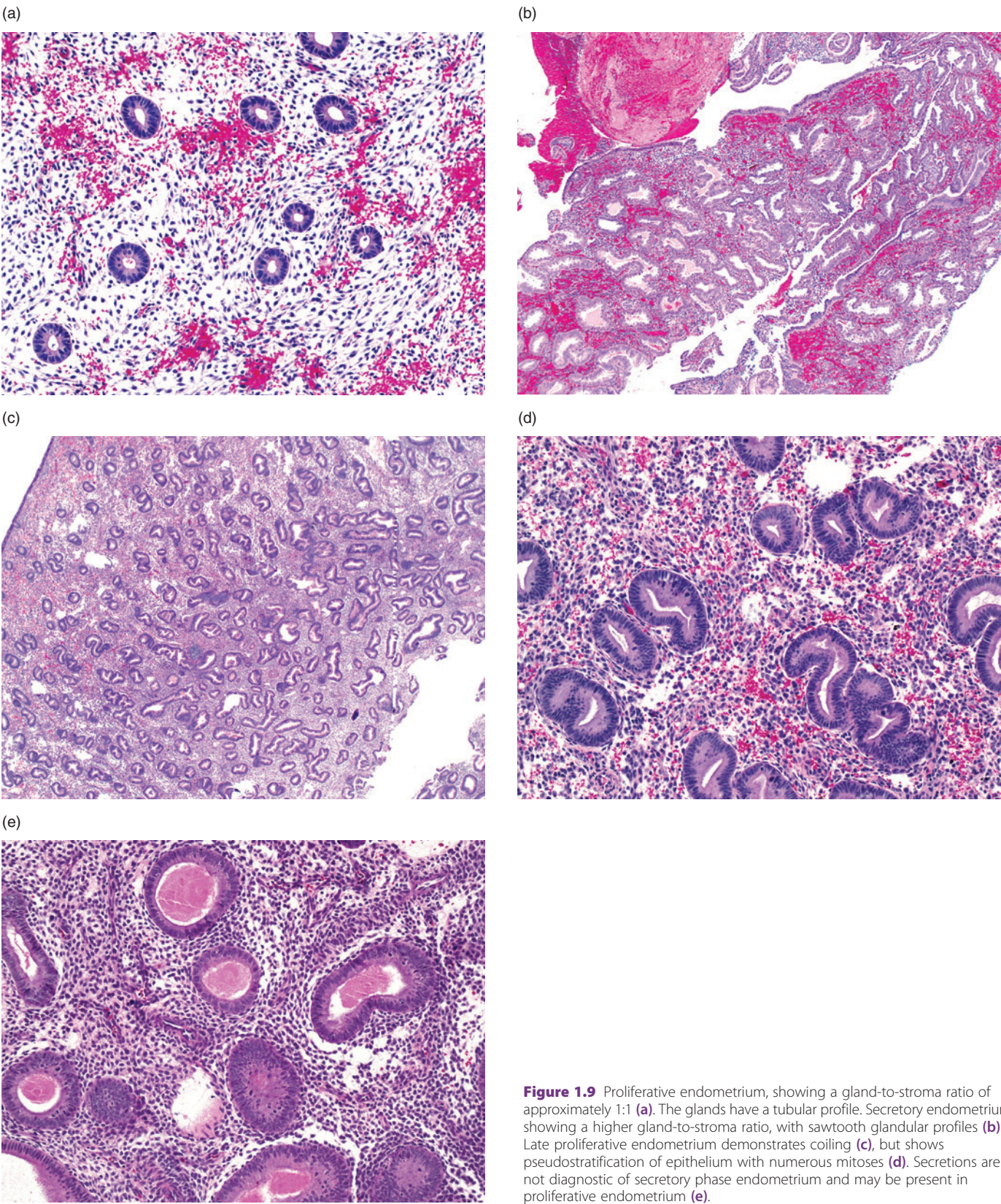
- 1. Endometrial sample with or without focal lesion with a gland-to-stroma ratio of approximately 1:1 or less (Chapter 2)
- 2. Endometrial sample with or without focal lesion with a gland-to-stroma ratio of 2:1 or higher (Chapters 3 and 4)
- 3. Endometrial sample with spindled (typically stromal) or myxoid lesion, largely devoid of glandular tissue (Chapter 5)
- 4. Endometrial sample with round cells (Chapter 6)
- 5. Endometrial sample with epithelioid cells (Chapter 7)
- 6. Endometrial sample with villous tissue (Chapter 8).

Glandular morphology and cytology

More detailed discussions of glandular morphology and cytology follow in subsequent chapters, and only the most basic rules are touched upon here. Although the glandular



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**Figure 1.9** Proliferative endometrium, showing a gland-to-stroma ratio of approximately 1:1 (a). The glands have a tubular profile. Secretory endometrium showing a higher gland-to-stroma ratio, with sawtooth glandular profiles (b). Late proliferative endometrium demonstrates coiling (c), but shows pseudostratification of epithelium with numerous mitoses (d). Secretions are not diagnostic of secretory phase endometrium and may be present in proliferative endometrium (e).



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and epithelial compartments are detailed separately, both components respond in tandem to hormonal stimulation, and in nonpathologic conditions there is harmony between the glandular and stromal elements. Endometrial glands morph from tubular in proliferative endometrium to coiled in secretory endometrium (Fig. 1.9a,b). However, coiling starts in proliferative endometrium, and late proliferative endometrium can superficially resemble secretory endometrium (Fig. 1.9c–e). In cross-section, proliferative glands appear circular to tubular, whereas secretory glands show a “sawtooth profile,” often with watery intraluminal secretions. However, intraluminal secretions are not diagnostic of “secretory endometria” and can be seen in proliferative glands (Fig. 1.9e). Abnormalities in gland architecture include alterations in shape (such as irregular shapes with budding and dilation to form cysts), as well as intraglandular architectural abnormalities (such as cribriforming, papillary, and other complex formations). Extensive budding appears as glandular crowding as groups of buds are cut in cross-section.

Proliferative glands are lined by pseudostratified epithelium (Fig. 1.10a). The nuclei are oval with coarse chromatin. Mitotic activity is prominent. In early proliferative endometrium, it is not uncommon to have admixtures of menstrual and proliferative endometrium, reflecting the re-epithelialization of the portion of endometrium shed earlier. Interval endometrium (days 15–16) is post-ovulatory endometrium, where progesterin-associated changes are not yet well developed. Subnuclear vacuoles may be present but the distribution is patchy, involving less than 50% of the epithelium, and mitotic activity is still present. In later stages (mid secretory endometrium), the glands acquire distinctive vacuolation that progresses from subnuclear (Fig. 1.10b) (day 17 – the earliest time period when there is histologic evidence of ovulation) to supranuclear (day 18). This is followed by discharge of secretion into glandular lumina. Secretory endometrial glands show more variability and the epithelium is usually nonstratified. Mid secretory endometrium is typically nonvacuolated cuboidal, with a round vesicular nucleus and small nucleolus (Fig. 1.10c). Late secretory endometrium demonstrates “exhaustion,” often with apoptotic nuclear fragments in the epithelium in response to hormone withdrawal. Mitotic figures (MFs) may be present in early secretory endometrium, but are typically reduced or absent in mid to late secretory endometrium.

In the absence of sufficient estrogenic stimulation, the epithelium becomes quiescent and can either appear as weakly proliferative (inactive) or atrophic (Fig. 1.10d; see also Chapter 2). These patterns are typically seen in postmenopausal women, but may also be seen with exogenous hormonal manipulation. It is also the typical pattern of lower uterine segment endometrium and basalis endometrium. Weakly proliferative endometrium shows a pattern intermediate between normal proliferative and atrophic. The epithelium is columnar, with only a minor degree of pseudostratification. MFs are few and far between. The nuclear chromatin is dense. Atrophic endometrial epithelium is low

cuboidal to flattened, with a single row of dense nuclei. Mitotic activity is absent. A variant of secretory endometrium is the hypersecretory endometrium, a response to the higher than usual levels of circulating hormones, such as seen in pregnancy. The cells show clear cytoplasm (hypervacuolation) or dense eosinophilic cytoplasm. When these changes are exaggerated, they are associated with nuclear pleomorphism and hyperchromasia (Arias-Stella reaction), and may be mistaken for malignancy.

Metaplastic changes are common in the endometrium and can be seen in both normal and abnormal endometrium, although metaplasia affecting large groups of glands is a feature of neoplastic endometrium. Hence, the finding of extensive metaplasia should raise flags for the pathologist. Detailed discussions of metaplasia are presented in subsequent chapters. The most commonly encountered metaplastic change is ciliated/tubal metaplasia (Fig. 1.11a). Although most authors use the terms interchangeably, in the strictest sense ciliated metaplasia refers to the presence of cells with cilia, whereas tubal metaplasia requires, in addition, the presence of interspersed clear peg (intercalated) cells. Eosinophilic change commonly coexists with mucinous and tubal/ciliated metaplasia (Fig. 1.11b). Squamous metaplasia presents in two forms: morular metaplasia and mature squamous metaplasia. Morular metaplasia is more common and typically takes the form of spherical aggregates of cytologically bland immature squamous cells. Central necrosis may be seen (Fig. 1.11c). It is uniformly CD10 and CDX2 positive and typically p63 negative (22–24). We have also noticed that it is p16 positive (Fig. 1.11d,e). Morular metaplasia is most commonly mimicked by gestational tissue with its dense pink fibrinoid (Fig. 1.11f). Mature squamous metaplasia, on the other hand, is p63 positive and typically CD10 and CDX2 negative. It may show hyperkeratosis, and when diffuse is referred to as ichthyosis uteri. It occurs in the setting of longstanding pyometra and may be associated with the development of primary endometrial squamous carcinoma (25). Historically, the lesion was seen in uteri treated with intrauterine formalin instillation for gynecologic disease. Other, less common metaplastic changes include mucinous, clear-cell, and hobnail metaplasia (Fig. 1.11g,h). Another “metaplastic change,” not really a metaplasia, is papillary syncytial metaplasia, which represents either a reparative–regenerative or regressive epithelial change associated with endometrial breakdown (26–29). Groups of eosinophilic epithelial cells are arranged in papillary and syncytial arrangements that are infiltrated by inflammatory cells and associated with stromal breakdown changes. Syncytial papillary metaplasia is positive for p16 and shows somewhat increased staining for p53, and can superficially resemble serous carcinoma (Fig. 1.12a,b).

Glandular cytology (discussed in greater detail in Chapters 3 and 4) should be evaluated in the context of architectural complexity and metaplastic changes and in comparison with “normal” glands if they are present. Lower levels of cytologic abnormality in a background of marked glandular complexity