Effects of Hormones

6

Contents

Women receive hormone preparations for a variety of reasons, including birth control and treatment for abnormal uterine bleeding, perimenopausal and postmenopausal symptoms, endometriosis, endometrial hyperplasia, endometrioid carcinoma, breast carcinoma, and certain types of infertility. Usually the exogenous hormone is some form of progestin, but estrogenic and even androgenic hormones are used for some disorders. Since the endometrium has estrogen and progesterone receptors, it shows the effects of these hormones.

An endometrial biopsy or curettage may be performed when abnormal bleeding occurs or when hormone therapy does not correct abnormal bleeding that is thought to be related to anovulatory bleeding. Sometimes, however, the biopsy is intended to evaluate the status of the endometrium following hormonal therapy, as in the case of hyperplasia managed with progestin therapy or routine follow-up of patients on hormone replacement therapy. In other circumstances, the endometrial sampling is coincidental with another procedure, such as tubal ligation, where the patient has received hormone therapy to ensure no interval pregnancy. The hormone, the dosage, and the duration of therapy influence the appearance of the endometrium. Clinical information regarding hormone use helps in the pathologic interpretation, but this history sometimes is incomplete when the specimen is received. Consequently, the possibility of exogenous hormonal effects should always be kept in mind.

This chapter reviews the effects of different types of hormones on the endometrium: (1) hormones used in women of reproductive age that clearly have estrogenic or progestogenic effects,

© Springer Nature Switzerland AG 2019
T. A. Murdock et al., *Diagnosis of Endometrial Biopsies and Curettings*,
https://doi.org/10.1007/978-3-319-98608-1_6

such as oral contraceptives; (2) estrogen–progestin hormone replacement therapy in postmenopausal women; (3) tamoxifen therapy for breast cancer; and (4) other hormones with less well-established effects on the endometrium.

Estrogenic Hormones

Estrogen therapy is largely used in perimenopausal or postmenopausal women to treat symptoms of menopause, such as vasomotor instability, genitourinary syndrome of menopause (previously termed atrophic vaginitis), and osteoporosis [1–8]. Estrogenic substances include conjugated estrogens, such as Premarin (Wyeth Pharmaceuticals, Collegeville, PA), micronized estradiol such as Estrace (Allergan Incorporated, Dublin, Ireland), or transdermal estradiols such as Vivelle-Dot (Novartis Pharmaceuticals Corp, East Hanover, NJ). Use of estrogenic hormones by themselves is associated with an increased risk of developing endometrial hyperplasia and endometrioid carcinoma, so the use of these hormones alone is now unusual in patients with a uterus. Consequently, the effects of unopposed exogenous estrogen are seen less frequently in biopsy specimens than the effects of combined estrogen–progestin compounds, as progestins abrogate the effect of estrogen stimulation on the uterus. Nonetheless, some patients do receive estrogen replacement only.

Unopposed estrogenic stimulation causes the endometrium to proliferate [9–12]. The result is variable, depending on the dose and duration of use. Often the pattern is that of proliferative phase endometrium, showing tubular to tortuous glands and abundant stroma. The patterns can be identical to those seen with anovulatory cycles and may include superimposed breakdown and bleeding (see Chap. 5). Continued, prolonged estrogenic stimulation can lead to disordered proliferative phase patterns and hyperplasia. Estrogen-related epithelial cytoplasmic changes, especially squamous differentiation and ciliated cell change, also often occur.

In some patients continued estrogen use leads to atypical hyperplasia and carcinoma [13, 14]. The risk of malignancy increases with the duration of therapy. After 1 year of treatment, low-dose unopposed estrogen was associated with a marginally nonsignificant increase in endometrial hyperplasia [15]. Unopposed estrogen use for 2–3 years significantly increased the risk of developing endometrial hyperplasia [15] and endometrioid carcinoma [16, 17]. The highest risk is in patients who have taken estrogens for 10 years or longer [16]. When carcinoma develops, it usually is low grade and superficially invasive, but high-grade lesions may occur.

All the estrogen-related changes are reviewed elsewhere in the text, including normal proliferative phase patterns (Chap. 2), proliferative with glandular and stromal breakdown (Chap. 5), hyperplasia and cytoplasmic change (Chap. 9), and carcinoma (Chap. 10). The reader should refer to those chapters for detailed morphologic descriptions of the specific entities.

Progestins, Oral Contraceptives, and Selective Progesterone Receptor Modulators

Although progestin effects are common, the subject of progestin-related changes is complex. Various forms of these synthetic analogues of progesterone, also termed “progestogens” or “progestagens,” are widely used, either alone or in combination with an estrogen. Progestin-only therapy is useful in the empirical medical management of abnormal uterine bleeding that clinically appears to be anovulatory. These hormones, such as medroxyprogesterone acetate or norethindrone acetate, suppress ovulation and endometrial growth. They also lead to secretory changes followed by gland involution and progesterone withdrawal bleeding, effecting a medical “curettage.” Consequently, progestins are especially helpful in managing ovulatory disorders where irregular, noncyclical endometrial growth results in abnormal bleeding. Often a trial of progestin is

given to alleviate apparent abnormal bleeding, and if the bleeding does not resolve, biopsy or curettage follows to exclude other structural pathology.

Progestins, usually given in combination with estrogens, are the basis for the oral contraceptive or "birth control pill." Most oral contraceptives are used in a fixed-dose formulation, with small doses of both the estrogen and progestin taken daily. Some oral contraceptives use a "phasic" combination with increasing amounts of progestin over a 21-day medication period. In either case the combination estrogen and progestin is administered over 3 weeks, and no medication is given in the 4th week to allow withdrawal bleeding to occur. Some oral contraceptives contain only progestin and are taken continuously without a hormone-free fourth week. The dose of progestin and estrogen used in modern oral contraceptives is much lower than that used in the initial formulations of oral contraceptives in the 1960s. Consequently, the pharmacologic effects of these steroid contraceptives are somewhat different than those originally described. Other combined hormone contraceptive methods include the etonogestrel/ethinyl estradiol vaginal ring, which is inserted vaginally for 3 weeks and the norelgestromin/ethinyl estradiol transdermal patch, which is placed on the skin weekly for 3 weeks. Both are removed following the third week, and similar to oral contraceptive pills, have a "hormone-free" fourth week.

Long-acting progestin-only contraceptive methods include a medroxyprogesterone injection every 12 weeks, the subdermally placed etonogestrel implant and the levonorgestrel intrauterine device (IUD), which are effective 3–5 years, respectively. The levonorgestrel-releasing intrauterine device may also be used to treat hyperplasia or endometrioid carcinoma of the endometrium. Other noncontraceptive benefits of hormonal contraception include cycle regularity, prevention of menstrual migraines; treatment of acne or hirsutism, leiomyomas, or endometriosis; and a decreased risk of endometrial, ovarian, or colorectal cancer [18–23].

The morphologic appearance of the endometrium following progestin therapy is variable and depends on the underlying status of the endometrium as well as the dose, potency, and duration of progestin therapy [12, 14, 24–26]. In fact, brief use of oral contraceptives for emergency contraception shows no significant histologic effects on the endometrium [27–30]. When used for emergency contraception, both levonorgestrel and the selective progesterone receptor modulator (SPRM), ulipristal acetate, act by delaying or inhibiting ovulation [31]. Ulipristal acetate (UPA) acts by reversibly blocking progesterone receptors and is also used as intermittent or preoperative treatment for women with uterine leiomyomas.

With more prolonged use of progestin, however, its effects can persist for several weeks to months following cessation of their use. To help simplify this complex subject, the effects of the progestins can be placed into three general morphologic patterns that form the basis for understanding the entire spectrum of progestin-mediated changes. These patterns include (1) decidual (pregnancy-like) changes, (2) secretory changes, and (3) inactive changes (Table 6.1). The pattern encountered depends on the degree of estrogen "priming" of the endometrium and the dose and duration of administration of the progestin. There often is an overlap between the various patterns of progestin effect in the endometrium.

Table 6.1 Morphologic features of progestin effects

Decidual (pregnancy-like) effects
Abundant tissue, often polypoid
Glands are predominantly inactive, but rarely show marked secretory activity
Stroma appears decidualized with lymphoid infiltrate
Vascular ectasia
Secretory effects
Moderate to sparse amount of tissue
Mildly tortuous secretory glands lined by columnar cells
Stromal cells are plump, oval (predecidual)
Vascular ectasia
Inactive effects
Sparse tissue
Glands are small and inactive, not coiled
Variable amount of stroma with plump to spindle-shaped cells

Patterns of Response

Decidual Pattern

The decidual or pregnancy-like pattern, as the term implies, features differentiation of endometrial glands and stroma to a point where they resemble the endometrium in pregnancy with decidual transformation of the stroma. Although the term "decidua" applies most strictly to the endometrium of pregnancy, this term also is useful for describing this progestin-induced pattern. This exaggerated effect typically occurs in endometrium which is influenced by high estrogen levels and therefore is actively growing and proliferating. This morphology is most common following high-dose progestin therapy for anovulatory cycles or for hyperplasia. In these cases the amount of tissue can be copious, and the biopsy or curettage can yield large polypoid tissue fragments. Although the tissue is polypoid, this finding does not indicate the presence of true polyps. With marked progestin effect, the stromal cells become enlarged and show abundant cytoplasm and prominent cell borders, resembling the decidua of pregnancy (Fig. 6.1). The stroma can show occasional mitotic figures. The glands are predominantly inactive, but with marked progestin effect, the glands develop a hypersecretory pattern with vacuolated cytoplasm and abundant luminal secretions. An Arias-Stella-like reaction with nuclear enlargement and hyperchromasia may occur in glands, but this is very rare. Some glands are dilated (Fig. 6.2). The spiral arteries also can show marked thickening with endothelial and smooth muscle hyperplasia [12]. The

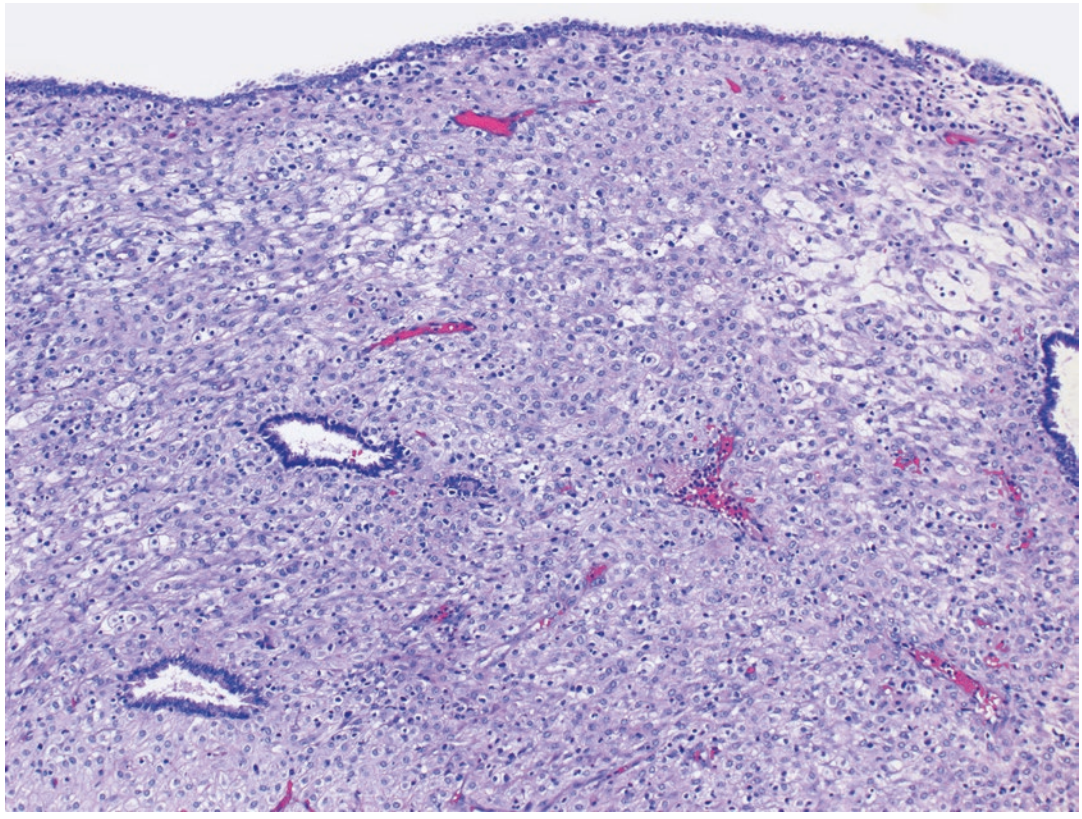

Fig. 6.1 Progestin effect, decidual pattern. Marked decidual reaction following progestin therapy of anovulatory bleeding. The changes resemble the endometrial decidual transformation in pregnancy. Inactive glands with secretory exhaustion are surrounded by abundant decidualized stroma

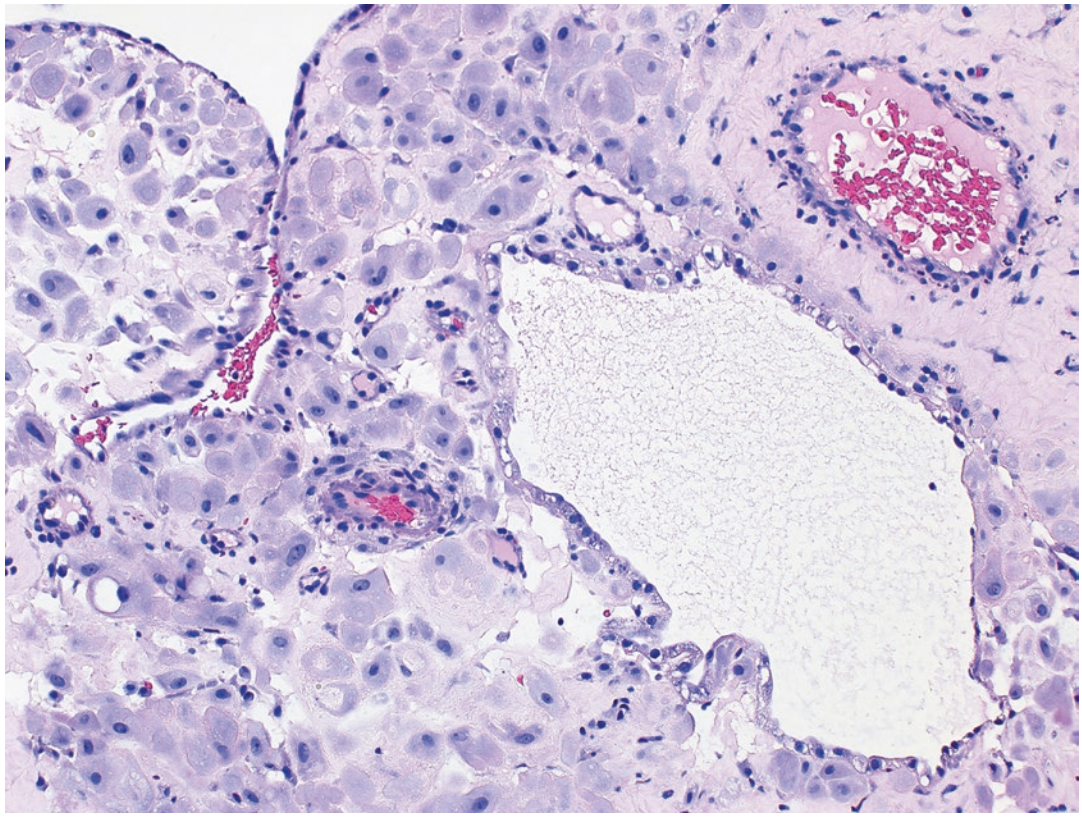

Fig. 6.2 Progestin effect, decidual pattern. Plump stromal cells with cystic dilation of a gland. The gland is lined by cuboidal epithelium with vacuolated cytoplasm. Signet-ring-like cells (lower left) and ectatic vessels are seen (courtesy of Dr. Chengbao Liu, The Johns Hopkins Hospital)

venules in the superficial portion of the endometrium become ectatic (Fig. 6.3). Often, especially in treated hyperplasia, the glands show prominent eosinophilic or mucinous cytoplasmic change [32]. Occasional cases of decidua-like progestin effect show prominent squamous change within glands. This change is usually seen in cases in which the biopsy results that led to therapy demonstrate hyperplasia, often with no squamous differentiation [26, 33].

Cases with advanced decidual changes often show areas of breakdown and bleeding, especially as the dilated venules thrombose. As a result, many of the features of breakdown and bleeding described in Chap. 5 are superimposed on the progestin effect. With breakdown, the collapse of the stroma and glands significantly alters their appearance, partially masking the patterns of development. In these areas of breakdown, the decidua-like character of the stromal cells is lost as the cells degenerate and lose cytoplasm. The glands fragment and become haphazardly oriented. Consequently, it remains important to avoid areas of active bleeding and find intact tissue in order to accurately assess the changes associated with the progestin effect.

Secretory Pattern

The secretory pattern of progestin effect mimics the glandular and stromal changes seen in the luteal (secretory) phase of the menstrual cycle. With the secretory pattern, the glands are tortuous, and the glandular cells have basally ori-

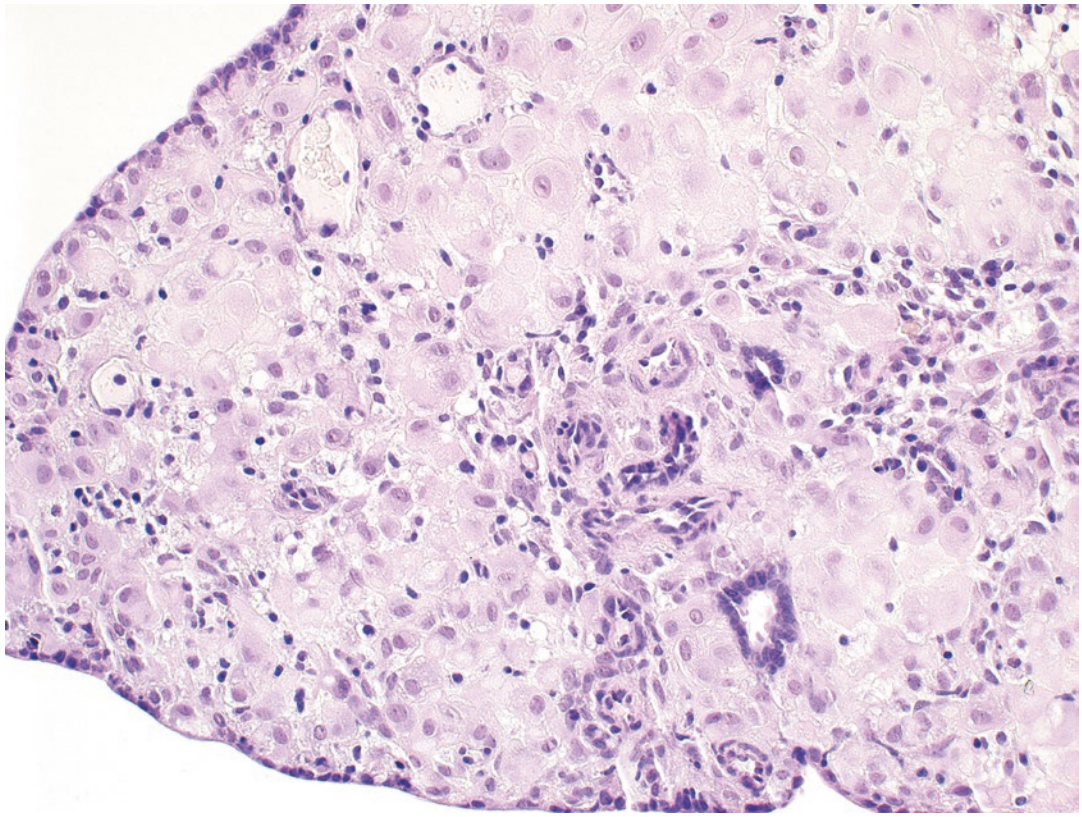

Fig. 6.3 Progestin effect, decidual pattern. Marked decidual change in the stroma and small inactive glands lined by a single layer of epithelium characterize the decidual pattern of progestin effect. Ectatic venules are present in the upper left of the field

ented nuclei (Figs. 6.4, 6.5 and 6.6). These low columnar cells typically have a small amount of pale-staining supranuclear cytoplasm and may show small, randomly distributed vacuoles. The apical border often becomes smooth and well defined, unlike the ragged luminal border in normal secretory endometrium [12]. The lumens may have a small amount of dense, eosinophilic secretions. The stromal cells show weak predecidual change as they gain cytoplasm and become mildly enlarged. These predecidualized cells are ovoid with identifiable pale cytoplasm but are not as large or polygonal as fully decidualized stromal cells. Although the glandular and stromal changes superficially resemble the secretory phase endometrium of a menstrual cycle, neither the glands nor the stroma are appropriately developed for any day of the normal cycle. Usually the glands appear to be underdeveloped, lacking tortuosity. Stromal predecidual change tends to be confluent, lacking the intermittent edema that characterizes most of the normal secretory phase. Scattered mitotic figures can be found in the stroma. As in other progestin-related patterns, the superficial stroma contains ectatic venules and may thrombose (Fig. 6.7).

Inactive Pattern

The inactive pattern represents the other end of the spectrum of progestin effect, in which the endometrium is hypoplastic. This pattern evolves following prolonged progestin therapy or with continued use of contraceptive hormones including levonorgestrel-releasing IUD and medroxyprogesterone acetate injection (Depo-Provera,

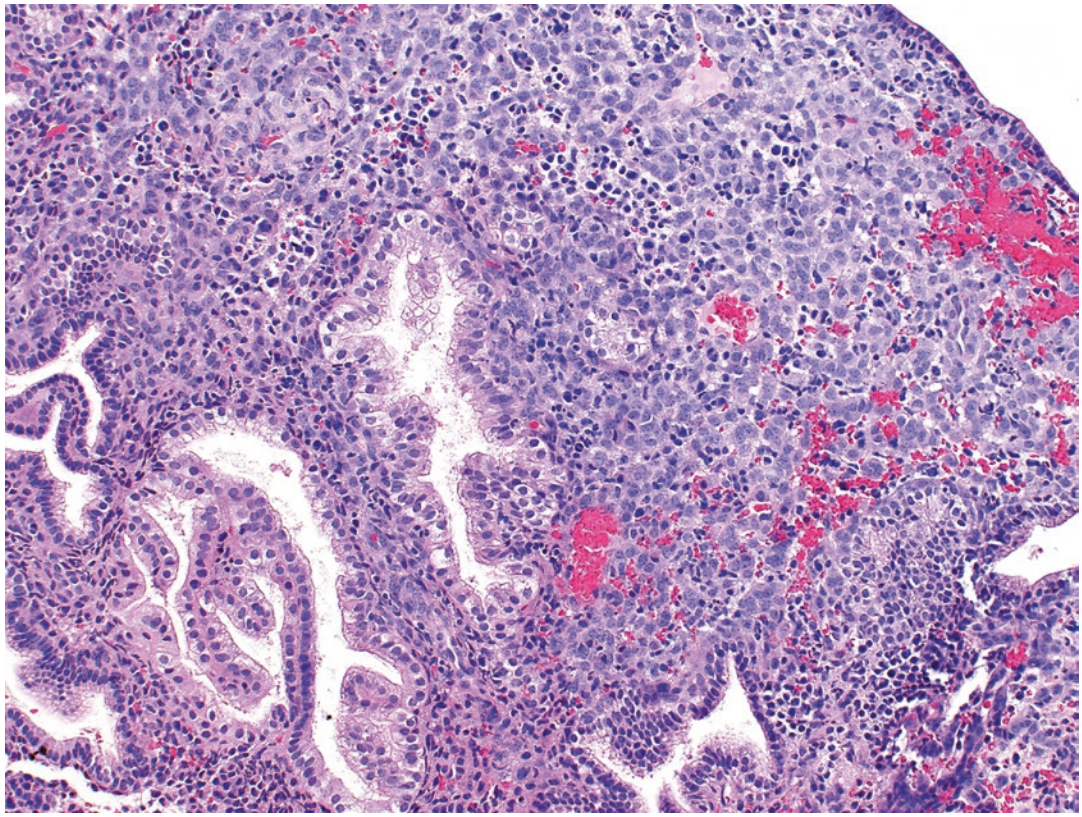

Fig. 6.4 Progestin effect, secretory pattern. The glands show marked secretory changes, and the stroma is transformed into decidua-like cells

Pfizer, New York, NY) (Fig. 6.8). The glands atrophy, although they continue to show weak secretory changes. The glands lose their tortuosity and are small and tubular with scant to absent luminal secretions. The epithelium is low columnar with basal nuclei and a small amount of pale cytoplasm.

When the progestin dose is low, the stromal cells remain mildly enlarged with a small amount of discernible cytoplasm but lose their decidua-like appearance (Fig. 6.9). Instead, they are plump and ovoid with only a moderate amount of cytoplasm. Cell borders become indistinct, and stromal mitoses are not found. Vascular channels beneath the surface epithelium become ectatic. In contrast to the physiologic atrophy pattern of the postmenopausal endometrium, progestin-induced atrophy often has more abundant stroma, while the glands become tiny and indistinct.

Other Stromal Changes

Whereas the glands atrophy with prolonged progestin effect, with high doses of progestin, the stroma retains a decidua-like appearance. In such cases the stroma can show alterations that can be confusing or alarming. For instance, the stroma can appear hyperplastic and pseudosarcomatous with increased cellularity as well as nuclear hyperchromasia, enlarged nucleoli, and variation in cell and nuclear size [12, 34, 35]. A pseudosarcomatous change is rare with modern progestin therapy, however, and is infrequent in our experience. The stroma can show other peculiar alterations. One change occasionally seen is clustering of groups of enlarged stromal cells with intervening areas of myxoid change or edema. This change can impart an epithelioid appearance to some of the decidualized cells, especially when

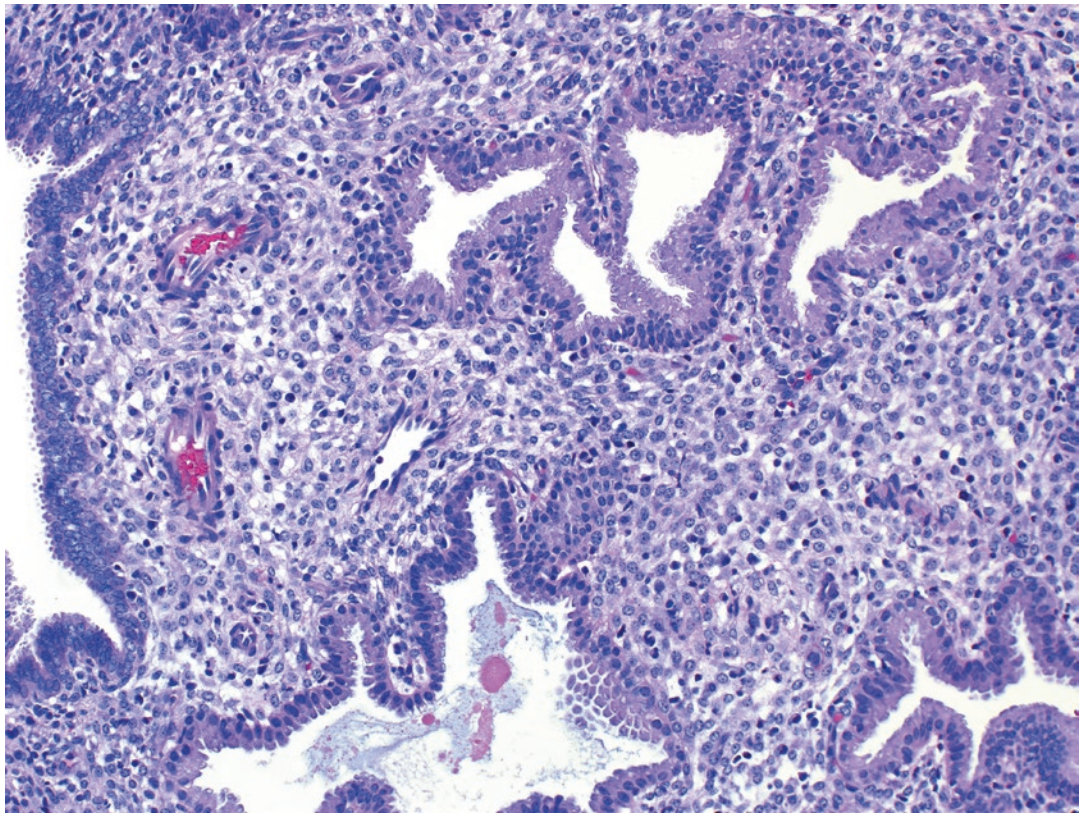

Fig. 6.5 Progestin effect, secretory pattern. High-magnification view of a pattern resembling secretory phase endometrium shows a tortuous gland with secretions. The stromal cells are plump, having a moderate amount of cytoplasm

the cells are enlarged with prominent cell borders. The decidualized stromal cells can develop other epithelioid features such as eccentric nuclei and vacuolated cytoplasm (Fig. 6.10) [36, 37]. In such cases the decidualized stroma can mimic signet-ring cells of metastatic carcinoma [37].

In some cases of progestin effect, infiltrates of lymphocytes or neutrophils yield patterns that can suggest endometritis (Fig. 6.11). For instance, with prolonged progestin effect of the levonorgestrel IUD, the stroma often contains a moderate infiltrate of stromal granular lymphocytes and mononuclear cells [38]. These are the normal lymphoid cells of the endometrium that appear exaggerated owing to the relative atrophy of the other components. This striking infiltrate can mimic chronic inflammation. An absence of plasma cells and no evidence of gland infiltration by inflammatory cells are helpful features to separate this progestin effect from true inflammation (see Chap. 7). Also, especially in pregnancy-like patterns of progestin effect, multiple small foci of breakdown are accompanied by a neutrophilic response. These neutrophils, however, are a localized response to tissue necrosis and do not represent an infectious process.

Often there is overlap between the various patterns of progestin effect, which depend on the duration of progestin use, the dose of the progestin, and underlying endogenous estrogen levels. In some cases, different fields from the same specimen show different patterns of progestin effect that can range from decidualized stroma to secretory or inactive change. Consequently, morphologic identification of progestin effects requires recognition of the spectrum of changes that may be found. Furthermore, some patients on progestins, especially those on oral contracep-

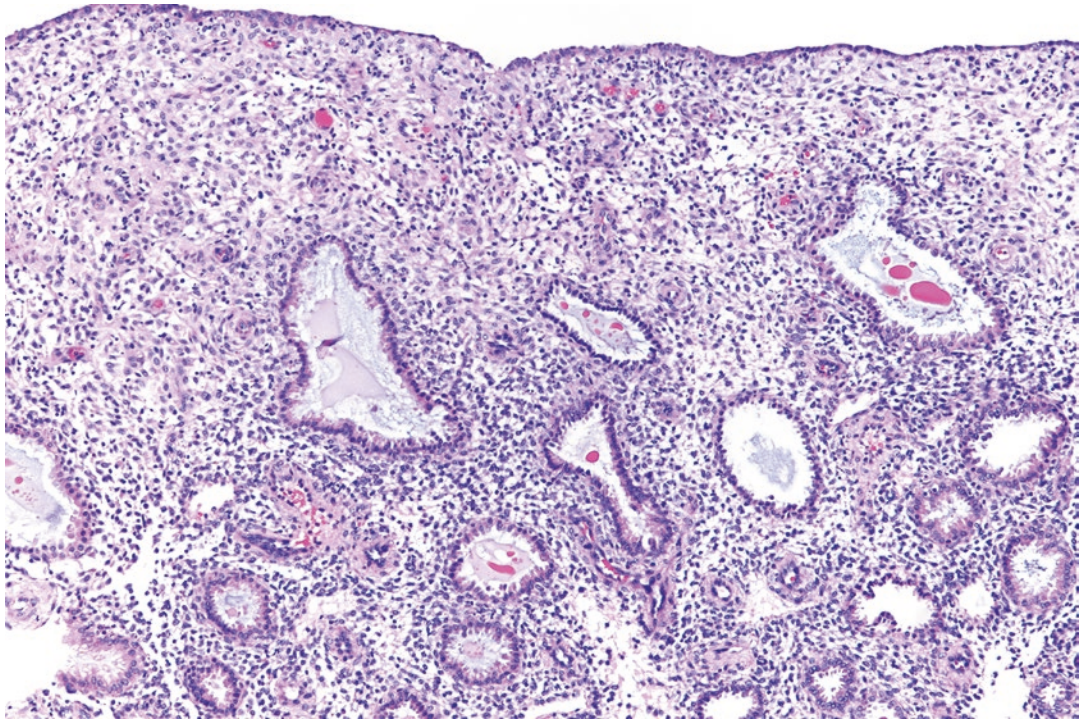

Fig. 6.6 Progestin effect, secretory pattern. The endometrium has some resemblance to secretory endometrium of the normal luteal phase with tortuous glands and abundant, predecidualized stroma. The amount of stroma is increased relative to the normal secretory phase. The glands, while slightly tortuous, are markedly underdeveloped relative to glands in the normal luteal phase

tives, can even show proliferative phase patterns when the estrogen influence is present, but the progestin influence is temporarily decreased or absent. Long-term use of oral contraceptives rarely may result in permanent endometrial atrophy after the agent is discontinued [39].

Combined Estrogen and Progestin as Replacement Therapy for Menopausal Women

Because of the possible deleterious consequences of unopposed estrogen therapy on the endometrium, estrogen replacement is nearly always given with a progestin in perimenopausal and postmenopausal patients with a uterus. Another treatment option is the combination of estrogen and bazedoxifene, a selective estrogen receptor modulator, which prevents bone loss and does not increase the risk of hyperplasia [40–42]. Combined estrogen–progestin hormonal replacement can be given either sequentially or in combination [43, 44]. The most common forms of estrogen prescribed are conjugated equine estrogens, synthetic conjugated estrogens, micronized 17β-estradiol, and ethinyl estradiol. Sequential medication uses daily estrogen for the first 21–25 days of the month and daily progestin added for the last 10–13 days. This regimen results in withdrawal bleeding. The continuous regimen uses both estrogen and progestin daily. In the continuous regimen, breakthrough bleeding may occur during the first 6 months, but then bleeding usually stops. Patients receiving either the sequential or the combined regimen may undergo biopsy as part of the routine surveillance to ensure that no neoplasm develops.

With the sequential estrogen–progestin regimen, the endometrium often shows a weakly proliferative

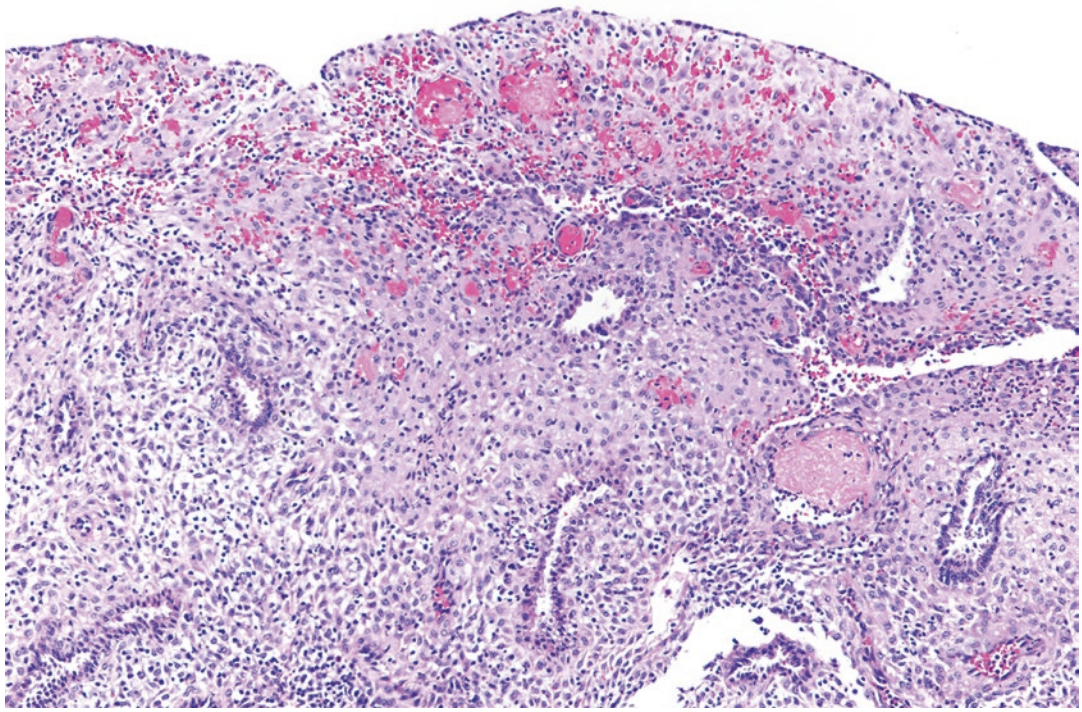

Fig. 6.7 Progestin effect, secretory pattern. Underdeveloped secretory glands in abundant stroma with decidual change near the surface. A thrombus is present to the right of center. Thrombi such as this result in bleeding that frequently leads to biopsy

pattern with small, tubular glands in scant stroma [45]. The epithelium can have occasional mitotic figures. The pattern is identical to the weakly proliferative phase pattern seen in association with anovulatory bleeding caused by estrogen withdrawal (see Chap. 5). Sometimes the tissue shows a superimposed progestin effect with poorly developed secretory changes in the glands (Fig. 6.12) [10, 46–48]. This latter pattern of secretory changes is especially likely to be seen if the biopsy is taken during the period of progestin administration. In these cases, the glandular cells show mild tortuosity, basal nuclei, some cytoplasmic vacuoles, and scant luminal secretions. In biopsy material, focal glandular and stromal breakdown also may be seen. With the combination regimens, and for that matter also with sequential therapy, the endometrium usually is inactive [26, 45, 46, 49–54]. Secretory changes can be seen especially if higher doses of estrogen and progestin are used [55]. Occasionally a patient receiving either the sequential or the combination regimen may have a more significant lesion in the biopsy specimen [53, 56–59]. Polyps, hyperplasia, and carcinoma are lesions that have been found in a few cases. In general, however, estrogen–progestin and estrogen–bazedoxifene replacement therapy control endometrial proliferation, and significant proliferative and neoplastic lesions are less common than in women not receiving this therapy [9, 45, 58, 60–64].

Progestin-Like Effects with No Hormone Use

On rare occasions endometrial tissue will show morphologic features of a progestin effect even though there is clearly no history of exogenous hormone use. These changes may be seen in both premenopausal and postmenopausal women, and their etiology is poorly understood. In premenopausal women, these patterns can be decidua-like [65] or

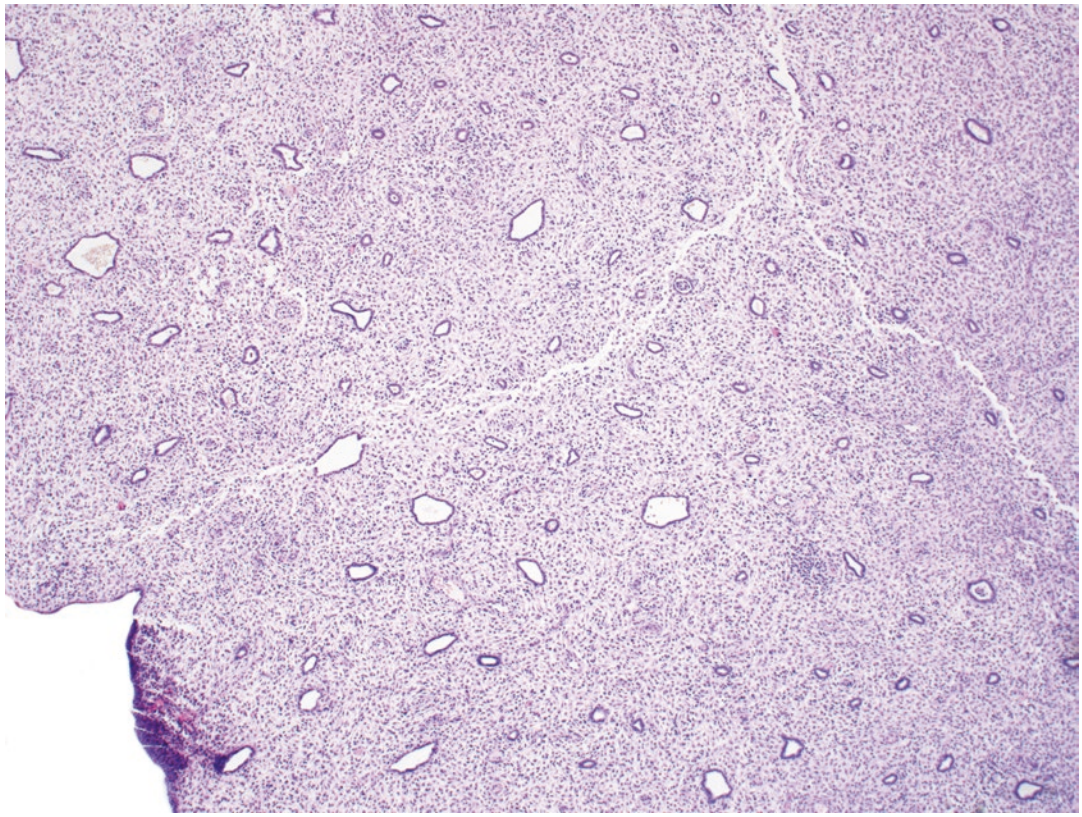

Fig. 6.8 Depo-Provera effect, inactive pattern. Small glands in abundant stroma; endometrium following long-term progestin use often has more abundant stroma while the glands become tiny and indistinct

can resemble "pill effect" changes, with hypoplastic secretory glands and plump stromal cells. It is possible that this alteration is due either to abnormal persistence of a functioning corpus luteum or to the so-called luteinized unruptured follicle. This latter entity, as the name implies, occurs when a follicle develops, does not rupture (ovulate), and persists with luteinization of the granulosa and theca cells. If progesterone is produced by the unruptured follicle, then the result could be a progestin effect from the endogenous source.

There have been a few examples of idiopathic endometrial decidual reaction in postmenopausal women who are not taking hormones [36]. These patients have tended to present with abundant polypoid tissue. The etiology of the change is not known, but it may be the result of local mechanical factors rather than a response to progesterone-like hormones. Mechanical stimulation, including biopsy, can cause increased decidual changes in the progesterone-primed endometrium [25, 66]. Also, an intrauterine device (IUD) may lead to an enhanced decidual reaction in the endometrium [25, 67, 68].

Effects of Other Hormones

Selective Progesterone Receptor Modulators

These drugs are used in management of endometriosis and uterine leiomyomas. Histologic changes can range from inactive and normal-appearing cycling endometrium to a spectrum of unique features [69]. With short- or long-term use of ulipristal acetate (UPA), a variety of non-physiologic changes can occur and given the

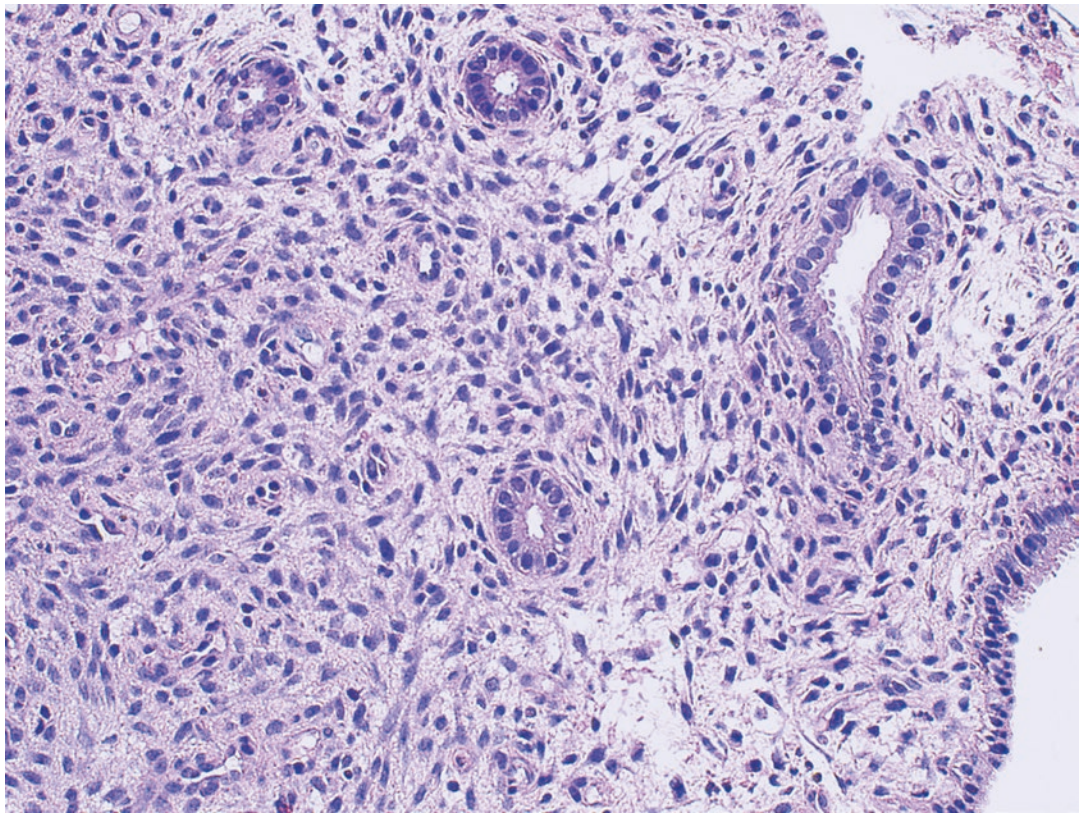

Fig. 6.9 Progestin effect, inactive pattern. Small inactive glands in spindle cell stroma show scant secretory changes. The abundant stroma, composed of plump cells with a moderate amount of cytoplasm, distinguishes this pattern from atrophy due to lack of estrogen. This pattern is commonly seen in women on continuous oral contraceptives

collective term "progesterone receptor modulator-associated endometrial change (PAEC)." These changes can include an increase in cystically dilated glands lined by flattened epithelium with low mitotic activity and apoptosis, while the stroma can be edematous or have a fibroblastic appearance resembling the stroma of endometrial polyps [70, 71]. The stromal vessels have a range of findings from "chicken-wire capillaries," to ectatic thin-walled or thickened walls with smooth muscle [70]. Because of the antiprogesterone effects of UPA, and therefore unopposed estrogenic effects, endometrial hyperplasia was observed in up to 1.1% of patients [70]. However, similar to the nonphysiologic findings, the hyperplasia regressed to benign 6 months following discontinuation of the drug [70, 72].

Tamoxifen

Tamoxifen is a nonsteroidal antiestrogen that is widely used in the hormonal therapy of breast carcinoma. This drug is a selective estrogen receptor modulator (SERM) with its action mediated through the estrogen receptor. The effect of tamoxifen on the endometrium appears to depend on the ambient estradiol concentration, menopausal status, and the dose and duration of tamoxifen use [73–75]. Current data suggest it can act as both an estrogen antagonist and an agonist [76]. Most normally cycling premenopausal patients taking tamoxifen continue to have regular menstrual cycles, but some develop amenorrhea. With continued use, serum estrogen and progesterone

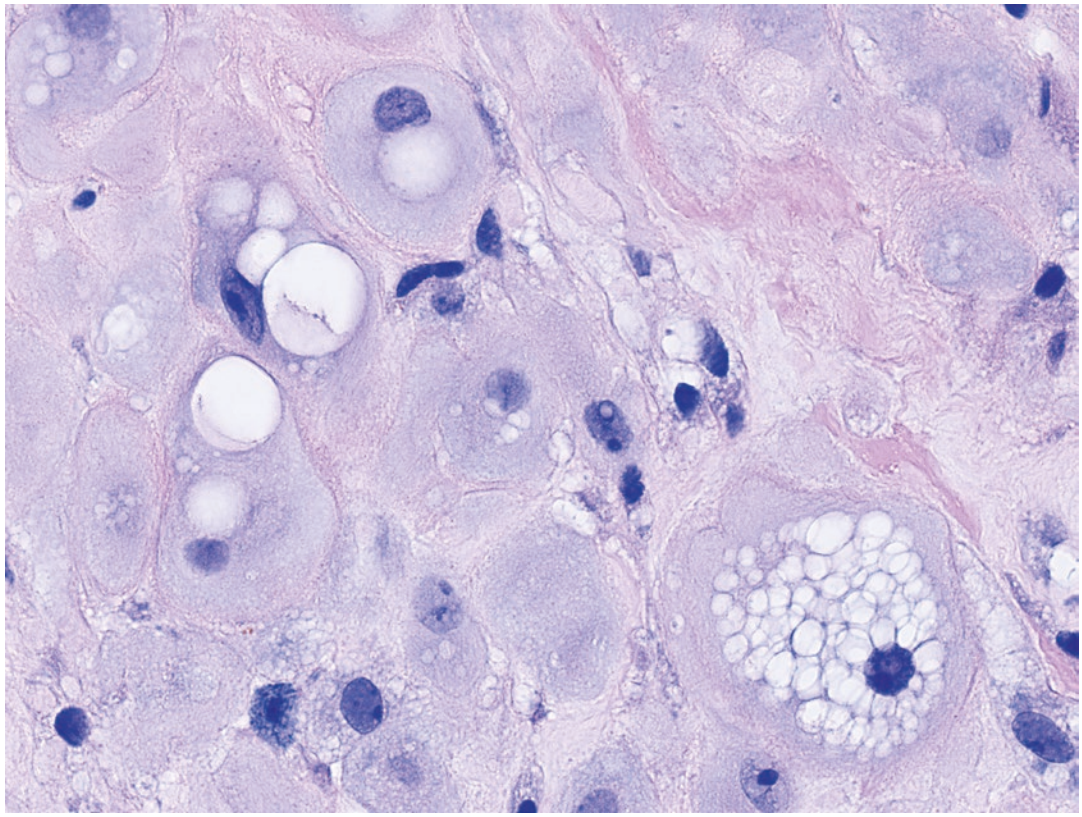

Fig. 6.10 Progestin effect, decidual pattern. The decidual cells have vacuolated cytoplasm and eccentric nuclei resulting in a signet-ring cell appearance

levels often are increased to two or three times the normal levels. In postmenopausal women, tamoxifen has estrogenic effects on vaginal epithelium.

A large volume of literature has accumulated on the effects of tamoxifen. Before beginning tamoxifen therapy, asymptomatic postmenopausal women with ER-positive breast cancer were found to have a high prevalence of subclinical endometrial abnormalities, including 29.6% with polyps (up to three polyps harbored simple hyperplasia) and 0.8% with endometrial hyperplasia [77, 78]. Baseline endometrial pathology correlated with increasing patient age, BMI, and time since menopause; therefore, endometrial screening in obese, older women before tamoxifen therapy may be useful [77, 78]. In general, postmenopausal women on tamoxifen should be monitored for symptoms of hyperplasia and carcinoma [79]. Premenopausal women on tamoxifen have no increased risk of endometrioid carcinoma, and routine gynecologic care is recommended [80]. Both transvaginal ultrasound and endometrial biopsy have been used to monitor patients on tamoxifen, and in the absence of symptoms, few pathologic lesions are found [81]. In asymptomatic postmenopausal patients on tamoxifen, atrophy is the most common finding [82, 83]. Endometrial abnormalities are more commonly found in symptomatic patients [82, 84], although some women with no symptoms or ultrasound abnormalities will be found to have a pathologic lesion [82, 85, 86]. Patients receiving a progestin after initial tamoxifen therapy can show decidual reaction of the stroma [87, 88].

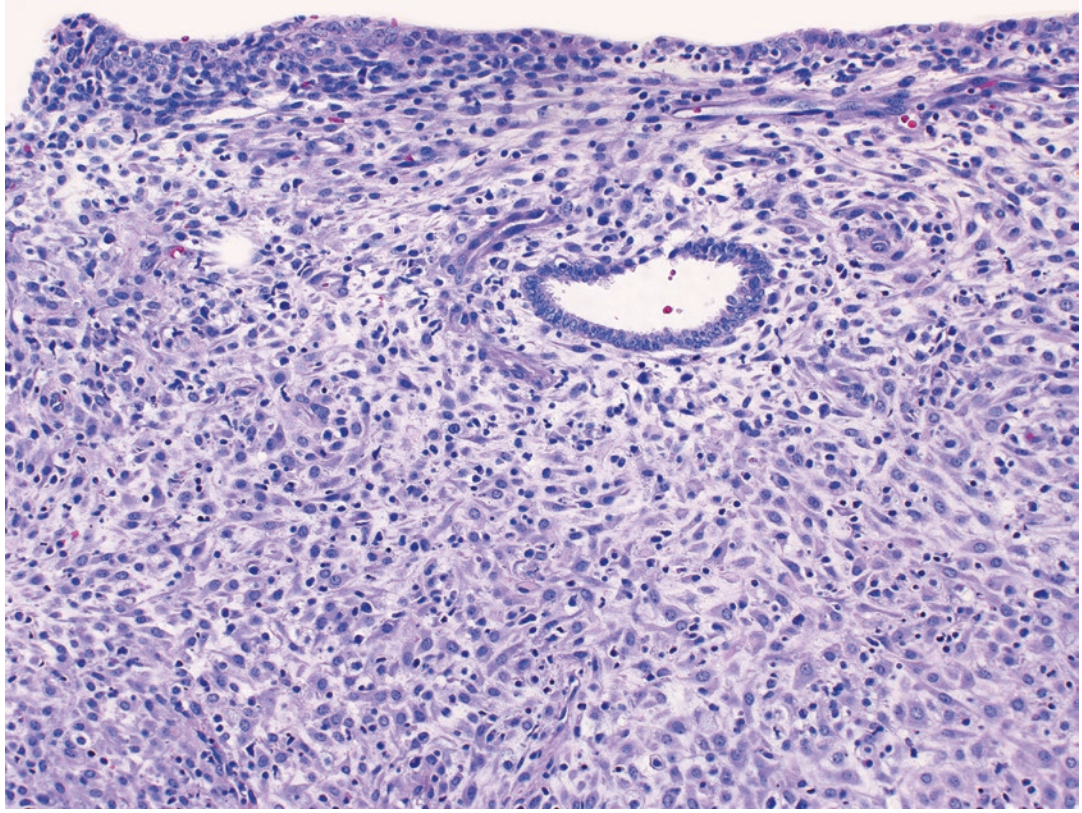

Fig. 6.11 Progestin effect. Abundant stroma containing a rich infiltrate of stromal granular lymphocytes mimicking an endometritis

Both endometrial hyperplasia and carcinoma occasionally occur in patients on tamoxifen, and some studies suggest an increased frequency of both these disorders in patients receiving tamoxifen [74, 79, 89–98]. The relative risk of developing endometrial carcinoma appears to be within the same range as reported with unopposed estrogen use [89]. The apparent increase may be the result of increased rate of detection of otherwise asymptomatic, "silent" tumors, however. There are conflicting results regarding the histologic grade of endometrial carcinomas that develop in women receiving tamoxifen treatment. Some patients develop high-grade carcinoma [91, 99–101], but most studies indicate those carcinomas associated with tamoxifen use do not differ in grade from carcinomas that occur in patients not receiving this hormone [91, 102, 103]. Most endometrial cancers are low stage and well differentiated [104]. When comparing tamoxifen to aromatase inhibitors (AI), another endocrine treatment for early breast cancer, vaginal bleeding, endometrial polyps, and atypical hyperplasia was more common in the tamoxifen treated group [105]. Carcinosarcomas (malignant mixed müllerian tumors [MMMTs]) and other sarcomas including endometrial stromal sarcoma and adenosarcoma also have been reported in patients on tamoxifen [106–109]. When comparing carcinosarcomas occurring in women with and without tamoxifen use, those with tamoxifen-related carcinosarcomas may have favorable tumor characteristics but comparable stage-specific survival outcomes [110].

Endometrial polyps appear to be one of the most common pathologic findings in patients on tamoxifen [73, 82, 99, 100, 105, 111–117]. These patients are postmenopausal and have

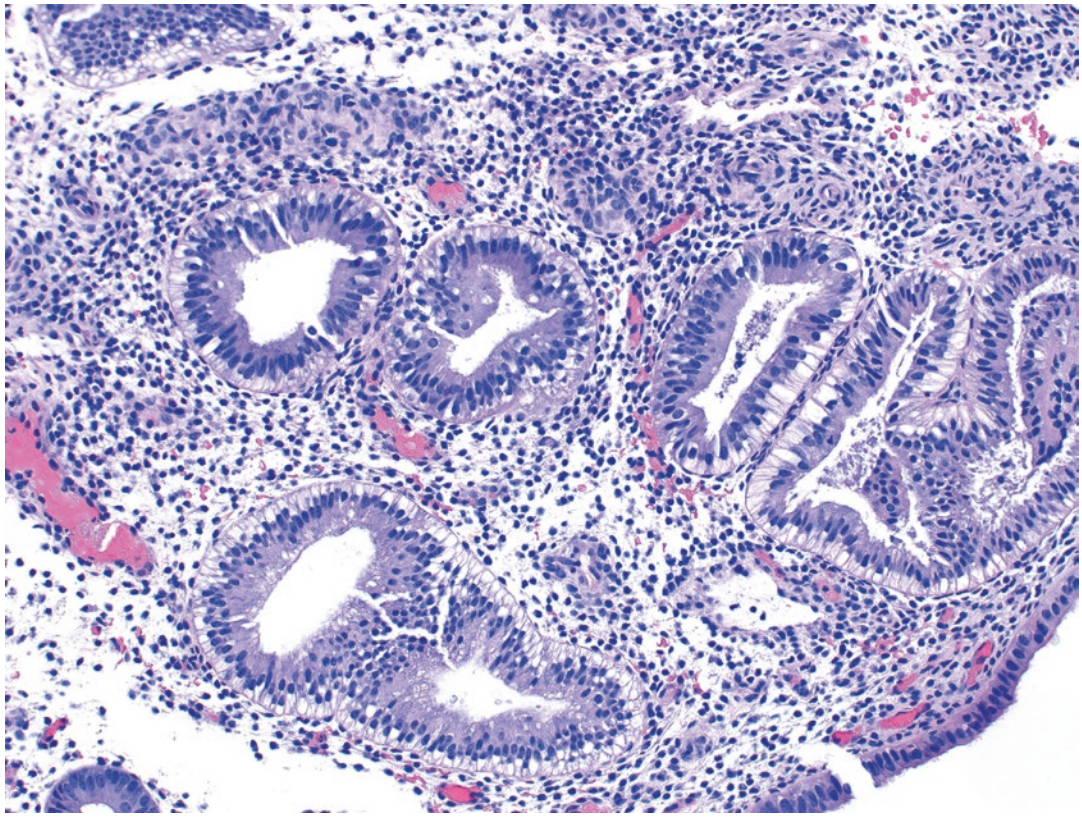

Fig. 6.12 Estrogen–progestin therapy. Endometrium from a postmenopausal woman receiving estrogen–progestin replacement therapy shows small secretory glands with extensive subnuclear vacuoles. This progestin effect resembles early secretory phase endometrium

received long-term tamoxifen therapy for metastatic breast carcinoma. The polyps tend to be large and multiple [118], and they may be recurrent [119]. The stroma is variably edematous, myxoid, or fibrous. Often these polyps show mildly hyperplastic changes (Fig. 6.13) (see Chap. 8). Various types of cytoplasmic change or metaplasia have been described in the glands, especially mucinous and clear cell change [114, 118, 120]. Occasionally endometrial polyps in patients receiving tamoxifen show foci of secretory changes in the glands with clear to vacuolated cytoplasm (Fig. 6.14). The mechanism of the secretory effects is not known. Some authors have found that the polyps show glands polarized along the long axis of the polyp with stag-horn-shaped glands and a cambium layer of stromal condensation around them [114]. In at least one reported polyp, the stroma also showed decidual changes that could not be attributed to any exogenous progestin use [112]. Some polyps, however, show markedly hyperplastic glands, and others show cystic glands with focal atypia [111, 112]. A few examples of atypical hyperplasia and carcinoma arising within these polyps also have been reported [100, 118, 121, 122]. The levonorgestrel intrauterine system was found to decrease the frequency of benign endometrial polyps and endometrial hyperplasia in women taking tamoxifen, but it was not clear if endometrial cancer was prevented [123]. With the expanding role of tamoxifen in the treatment and possible prevention of breast carcinoma, more clinical information will be accumulated regarding the effect of this drug on the endometrium.

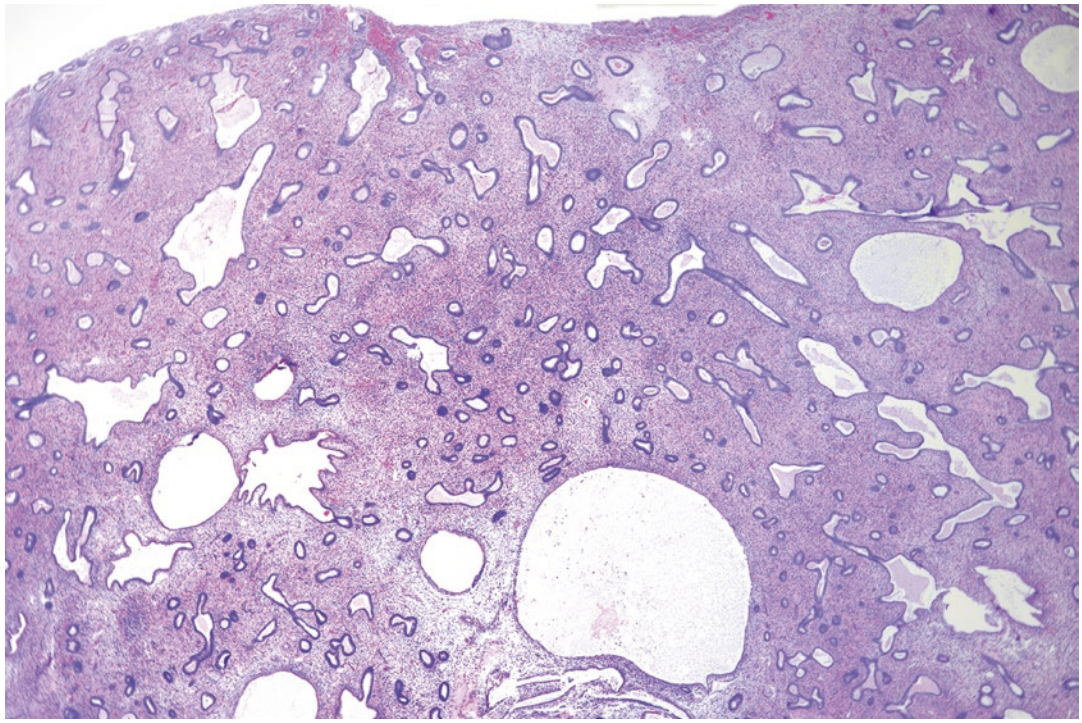

Fig. 6.13 Tamoxifen-related polyp. Portion of a large polyp removed by curettage in a postmenopausal patient on tamoxifen for breast carcinoma. The glands have irregular, staghorn shapes and showed weak proliferative activity. The stroma varies from fibrous to edematous

Raloxifene

Raloxifene is another selective estrogen receptor modulator (SERM) and may be useful in preventing postmenopausal osteoporosis. This drug appears to be a more pure estrogen antagonist, lacking the weak estrogen agonist effects of tamoxifen [124, 125]. When compared to placebo, raloxifene showed no difference in the incidence of ovarian cancer, postmenopausal bleeding, endometrial hyperplasia, or carcinoma [126]. In comparison to those receiving tamoxifen, there appears to be no increase in endometrial pathologic lesions with raloxifene [127–130]. In patients diagnosed with endometrial cancer in the general population, tamoxifen compared to raloxifene users were three times more likely to develop endometrial cancer [131]. In that same population, the risk of endometrial cancer was 50% less among raloxifene users compared to nonusers [131]. Usually the endometrium is inactive.

Clomiphene Citrate

Clomiphene citrate is another SERM that is used to induce ovulation in the treatment of infertile patients who are anovulatory [1]. This hormone stimulates multiple follicles to develop, and ovulation follows. It is thought to act by competitively binding to estrogen receptors in the hypothalamus, causing increased levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) that induce ovulation. Like tamoxifen, clomiphene citrate has been found to have estrogenic as well as antiestrogenic activity.

Morphologic effects of clomiphene on the endometrium are difficult to assess. Biopsies often are performed in the luteal phase of clomiphene-induced cycles to assess the endometrial development. Usually the pattern is that of normally developing secretory phase endometrium. One study of the morphologic effects of clomiphene citrate on the endometrium suggested that the drug

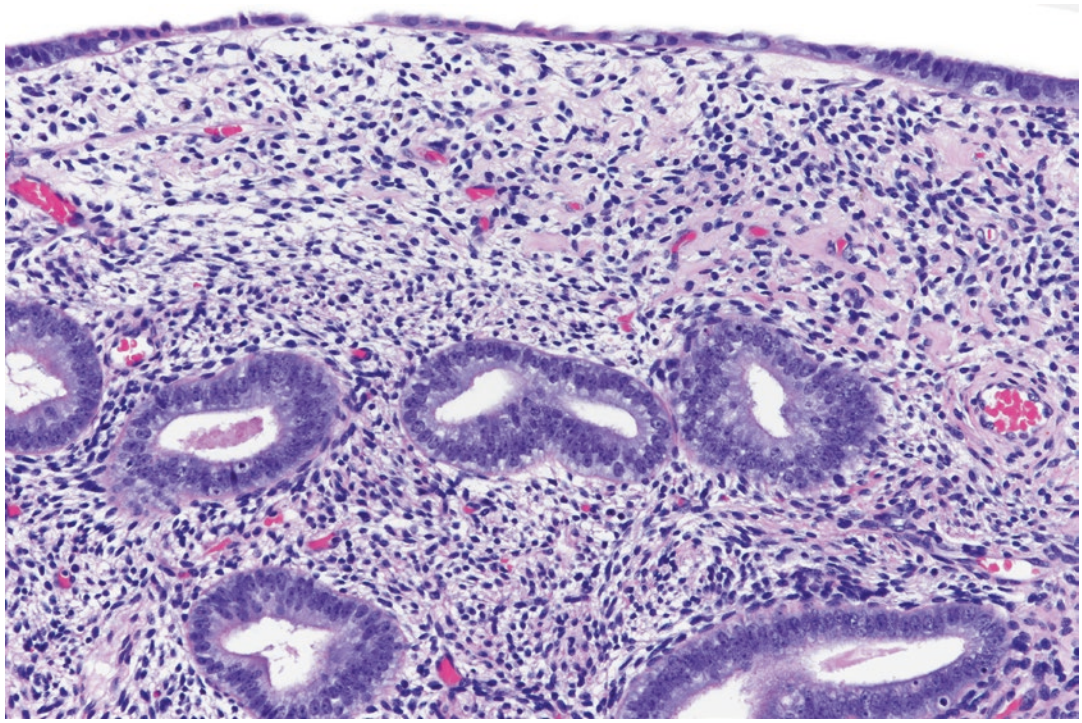

Fig. 6.14 Tamoxifen effect with secretory change. Endometrial biopsy from a woman with breast cancer shows weak secretory effect manifested by small cytoplasmic vacuoles

causes significant alterations in secretory phase development [132]. Decreased gland tortuosity with scant secretions in clomiphene-treated cases was described. The gland-to-stroma ratio was reportedly decreased relative to secretory endometrium in untreated women. In early secretory endometrium, the subnuclear vacuoles appeared to be larger and more sharply defined, and later in the secretory phase, the luminal secretions appeared to be hyalinized and inspissated. The stroma also showed decreased predecidual change compared to untreated endometrium. This report suggests that clomiphene may cause reproducible morphologic changes in secretory phase endometrium. Another study reported advanced secretory activity in clomiphene citrate-induced cycles [133]. Other investigators have found no changes in endometrial morphology following clomiphene citrate administration [134–136]. In our opinion, any morphologic changes associated with clomiphene citrate are subtle and difficult to appreciate by routine microscopy.

Danazol

Danazol is structurally related to testosterone and is a weak androgen [137]. Its main metabolite, ethisterone, is a weak progestin, however [138]. This steroid is used for the treatment of endometriosis [1]. Because it suppresses endometrial growth, it also may be used to treat heavy menstrual bleeding [139–142], symptomatic leiomyomas [142], and endometrial hyperplasia [143, 144]. The side effect profile of acne, hirsutism, and weight gain makes it a less desirable treatment option [139].

The few studies of the effects of danazol on the endometrium show changes similar to those found in progestin therapy [138, 145, 146]. Within a few months of use, the amount of tissue is reduced [147]. Glands show weak and irregular secretory changes with mild tortuosity, basal nuclei, and some cytoplasmic vacuolization. The stroma is hypercellular. With prolonged therapy, the glands become inactive with scant to no

secretory activity [137, 146–148]. Vascular ectasia also can occur [149]. Occasionally there is some proliferative activity with stromal and glandular mitoses.

Human Menopausal Gonadotropins/ Human Chorionic Gonadotropin

Human menopausal gonadotropins (hMG or menotropins) are extracted from the urine of postmenopausal women and consist of FSH and LH. These drugs are used to induce ovulation in the treatment of infertility due to anovulation, such as polycystic ovarian disease. Human chorionic gonadotropin (hCG) has structural and biologic similarities to LH and is used to simulate and improve on the midcycle LH surge associated with ovulation. This hormone is used in conjunction with hMG and can be used along with clomiphene citrate-induced ovulation.

The effects of hMG and hCG on endometrial morphology are difficult to define. Some studies suggest that the main change caused by administration of hMG/hCG is endometrial "inadequacy" with delayed development of more than 2 days when the histologic date is compared to the chronologic date [150–153]. In one study, 27% of patients treated with hMG/hCG showed inadequacy in development with out-of-phase histologic dates [150]. Other studies, however, have reported "advanced" histology with more highly developed secretory changes than expected for the cycle day, gland-stromal dyssynchrony, or normal glandular development [154, 155]. Despite the apparent discrepancies in the findings between studies, there are no specific morphologic alterations that can be definitely correlated with the effects of these hormones. There is a positive relationship between endometrial thickness and clinical pregnancy with in vitro maturation (IVM) treatment [156]. When comparing low-dose human menopausal gonadotropin and micronized 17beta-estradiol supplementation to improve endometrial thickness during IVM, both showed significant improvement in endometrial thickness, but hMG had the additional advantage of larger ovarian follicles and a greater number of in vivo matured oocytes [157]. For the pathologist interpreting biopsies from women who receive these hormones, accurate histologic classification into early, mid or late secretory phase is the most important consideration.

Gonadotropin-Releasing Hormone Agonists

Gonadotropin-releasing hormone (GnRH) agonists include leuprolide acetate, buserelin acetate, and goserelin acetate. They are also referred to as "luteinizing hormone-releasing hormone agonists." These preparations are used to suppress the endometrium prior to resectoscopic ablation and to decrease the size of leiomyomas before surgical removal [158, 159]. They are also used to prevent spontaneous LH surges before oocyte retrieval and to improve follicular development for ovulation induction during in vitro fertilization (IVF) and gamete intrafallopian transfer (GIFT) [1]. In conjunction with progestins, these compounds may also have utility for contraception. When they are used to suppress endometrial growth, GnRH agonists cause marked atrophy of the endometrium [141, 149]. When GnRH agonists are used in conjunction with a progestin, the endometrium shows apparent secretory changes consistent with progestin effect [160].

Antiprogestin RU486

The synthetic progestogenic steroid RU486, or mifepristone, has high affinity for progesterone receptors in the endometrium, which causes its antiprogesterone action [161]. Its main use is for medical abortion, which involves the use of medications rather than a surgical procedure for termination of early pregnancy. The effects on the uterus include necrosis of the capillary endothelium [162] and decidua [161] uterine contractility and sensitivity to prostaglandin [163]. The drug is used in high dose to induce early abortion and is most effective up to 63 days of gestation (calculated from LMP). The more common regimen is oral administration of mifepristone followed

by misoprostol, a prostaglandin E_1 analogue, 48 h later.

Mifepristone also has been used to treat leiomyomas and pain in women with endometriosis [164]. Daily administration has contraceptive potential and has been shown to block ovulation [165, 166]. Studies suggest that with longer-term use, the secretory phase is not appropriately developed [161, 167–174].

One case report of an adolescent female osteoporosis treated with high-dose mifepristone for its antiglucocorticoid effect describes recurrent diffuse simple hyperplasia of the endometrium [175]. Controversy has been associated with the histological effects on women receiving low-dose mifepristone for 6 months for the treatment of fibroids. One study reported simple non-atypical hyperplasia in 28% [176]. A National Institutes of Health sponsored workshop evaluated the effects of mifepristone (including the specimens from the aforementioned study), asoprisnil, ulipristal acetate, and JNJ-17072341. Premalignant lesions such as atypical hyperplasia/EIN were not identified. There was a subset of cases with asymmetry of stromal and epithelial growth resulting in prominent cystically dilated glands with admixed estrogen (mitotic) and progestin (secretory) effects [69, 177]. These effects are consistent with progesterone receptor modulators (PRM) and the previously mentioned PRM-associated endometrial changes (PAEC) in the ulipristal acetate section above. In postmenopausal women receiving estrogen alone, this drug has effects similar to those of progesterone, suggesting it acts as a progesterone agonist [161, 167, 168, 178].

Clinical Queries and Reporting

A wide variety of indications for hormone use influence the reasons for biopsy and the clinical questions posed to the pathologist. Most biopsies that show hormone effects are performed for one of the following reasons: (1) surveillance during postmenopausal hormone replacement therapy, (2) evaluation of abnormal uterine bleeding related to hormone therapy, (3) assessment of treatment of hyperplasia or carcinoma, and (4) evaluation of the status of the endometrium following hormone induction of ovulation or endometrial growth in infertility therapy. For each of these indications, there are specific considerations in interpretation and reporting.

Postmenopausal Hormone Replacement

Surveillance biopsy of asymptomatic postmenopausal patients receiving estrogen or estrogen–progestin replacement therapy usually is an office-based procedure intended to provide a small representative sample. The primary concern is whether the endometrium shows evidence of hyperplasia or neoplasia that would require cessation or change of the hormone therapy. The presence or absence of these changes should be explicitly stated in the report. This information can appear either in the diagnosis or as a comment. In these cases, accurate reporting of the degree of proliferative activity, if any, also is important.

Abnormal Uterine Bleeding

There are several situations in which hormone therapy is related to abnormal bleeding. Sometimes patients on oral contraceptives or other progestins experience “breakthrough bleeding,” which indicates bleeding of a noncyclical type. This may occur as irregular bleeding during the first few months of oral contraceptive use or later after many months of oral contraceptive use. Often the bleeding is caused by glandular atrophy and increased “fragility” of the tissue with focal glandular and stromal breakdown. In other situations, hormone therapy may be used as primary therapy for abnormal bleeding, especially AUB due to ovulatory dysfunction (see Chap. 5). Usually these patients have anovulatory cycles, and a progestin is given to suppress proliferation. If the bleeding is not controlled by progestin, then curettage is performed.

Other hormone therapies may also lead to abnormal bleeding. For example, tamoxifen ther-

apy for breast cancer, or estrogen replacement therapy for menopausal symptoms, may be associated with bleeding. Biopsy in such cases is performed to rule out significant structural lesions. Also, megestrol acetate (Megace) therapy for breast cancer may lead to decidual transformation of the endometrium with focal glandular and stromal breakdown. In any of these cases in which hormone therapy is associated with abnormal bleeding, the biopsy is performed to assess the status of the endometrium and to rule out possible underlying inflammation or structural disorders such as polyps, hyperplasia, or neoplasia. In addition, the biopsy may be therapeutic, removing the abnormal tissue that is bleeding. Most of these biopsies show progestin effects that range from decidual patterns to inactive patterns. When the patient has received unopposed estrogen, however, the pattern usually is proliferative. A specific diagnosis should be rendered. If this is not possible, a descriptive diagnosis should be made. When glandular and stromal breakdown also is present, this should be reported. In all these cases, it is important to exclude other lesions such as hyperplasia or carcinoma, so a comment regarding the absence of these lesions is generally indicated.

Treatment of Hyperplasia and Endometrioid Carcinoma

Hyperplasia, either with or without atypia, may be managed by progestin therapy to suppress gland growth and then re-biopsied to determine the efficacy of the therapy. In these cases, it is important to note whether or not there is evidence of continued persistent hyperplasia and whether or not atypia is found. In progestin-treated hyperplasia, the underlying pattern of gland growth and cellular differentiation often becomes distorted. Frequently the tissue resembles that seen in early pregnancy. When there is a well-developed decidua-like response, it is difficult to fully assess the degree of gland complexity, and the secretory changes of the glands make evaluation of cytologic atypia difficult or impossible. Generally, cytologic atypia and mitotic activity are suppressed by progestin treatment, and the gland cells show rounded nuclear contours, condensed chromatin, and loss of nucleoli. It is important to state clearly that progestin effect is present and that it may not be possible to assess fully the degree of the glandular abnormality. An effort also should be made to review the previous material to assess the effect of the therapy on the hyperplasia.

Studies have evaluated the effect of progestin therapy on complex atypical hyperplasia and well-differentiated endometrioid carcinoma to assess features that would predict the effectiveness of the therapy [32, 179]. These patients often are poor surgical candidates or wish to preserve fertility if premenopausal. Most patients were treated with an oral progestin or a progestin-releasing IUD. In women with a pre-treatment diagnosis of complex atypical hyperplasia (CAH), progestin therapy generally decreases the glandular crowding and complexity of the individual glands; however, small foci of glandular confluence (cribriform pattern) may be present [179]. Metaplastic changes including eosinophilic, squamous, and mucinous changes are frequent [179]. In women with a pre-treatment diagnosis of well-differentiated carcinoma, glands displaying complex outlines and confluency (cribriform and/or papillary patterns) are often present and may be more pronounced in post- rather than pre-treatment samples [179]. Cytoplasm is usually eosinophilic, and the metaplastic changes are similar to those encountered in progestin-treated CAH [179].

To fully evaluate the response to treatment, it is important to review the pre-treatment biopsy and all subsequent posttreatment specimens available for review [179]. This is important because studies found that most cases showed resolution of the process, but persistence of cytologic atypia and architectural abnormalities after 6 months of therapy were associated with treatment failure. One study, however, did find that confluent or cribriform gland patterns did not imply disease persistence or progression and that only cytologic atypia was important in determining treatment failure [32]. That study also noted that eosinophilic and mucinous cytoplasmic

changes were frequently seen following progestin therapy and occasional cases also showed squamous change. See Chap. 9 (Endometrial Hyperplasia, Endometrial Intraepithelial Carcinoma, and Epithelial Cytoplasmic Change) and Chap. 10 (Endometrial Carcinoma) for further details.

Infertility Therapy

When a biopsy is done during hormone therapy in the infertile patient, the clinical questions depend on the hormone used and the indication for biopsy. Often before beginning treatment, the clinician would like to rule out a structural cause for infertility such as endometrial polyps, uterine septa, submucosal leiomyomas, chronic endometritis, or endometrial hyperplasia or carcinoma. During treatment with a drug, such as clomiphene citrate, the reproductive endocrinologist or gynecologist wishes to know whether secretory phase development has occurred (see Chap. 2). When ovulation-inducing medication is used, one obvious question is whether the endometrium shows secretory changes that reflect ovulation or if the pattern is proliferative. Historically, this determination required accurate histologic dating of secretory endometrium (see Chap. 2). However, when the clinician requests accurate dating of secretory phase endometrium, a diagnosis of early, mid-, or late secretory phase endometrium is recommended [180].

In addition to the specific situations for hormone use given in the preceding, hormone effects, especially progestin-related changes, can be found in other biopsy specimens when the hormone use is incidental. These cases include biopsies performed during evaluation of pelvic pain, pre-hysterectomy sampling, or curettage at the time of tubal ligation. Furthermore, progestin effects can persist for a variable period of one or more months after the drug is discontinued. Occasionally, some of these cases may represent an endogenous progestin effect with no exogenous hormone use. Consequently, the finding of the histologic changes of apparent progestin effect is not negated by the clinical history. When the biopsy clearly shows a progestin effect, we recommend a brief description of the gland and stroma changes followed by the term "consistent with exogenous hormone therapy effect" as the diagnosis. For example, "Inactive decidualized endometrium, consistent with exogenous hormone therapy effect."

In some cases the glands and stroma show some changes that suggest progestin effect but the features are not diagnostic. Usually these cases show glands with poorly developed secretory changes and plump stromal cells that appear to be partly decidualized. If the clinical history does not establish progestin use and the changes by themselves are not diagnostic of progestin effect, then it is best to give a descriptive diagnosis. This diagnosis can reflect the fact that irregular secretory changes are present and suggest the possibility of progestin effect. A descriptive diagnosis would serve to indicate that the changes are benign and caused by an imbalance in the amounts of sex steroid hormones, regardless of their source.

References

1. Fritz MA, Speroff L. Clinical gynecologic endocrinology and infertility. 8th ed. Philadelphia: Lippincott Williams & Wilkins; 2010.
2. Maclennan AH, Broadbent JL, Lester S, Moore V. Oral oestrogen and combined oestrogen/progestogen therapy versus placebo for hot flushes. Cochrane Database Syst Rev. 2004;18:CD002978.
3. Greendale GA, Reboussin BA, Hogan P, Barnabei VM, Shumaker S, Johnson S, Barrett-Connor E. Symptom relief and side effects of postmenopausal hormones: results from the Postmenopausal Estrogen/Progestin Interventions Trial. Obstet Gynecol. 1998;92:982–8.
4. Cintron D, Lahr BD, Bailey KR, Santoro N, Lloyd R, Manson JE, Neal-Perry G, Pal L, Taylor HS, Wharton W, Naftolin F, Harman SM, Miller VM. Effects of oral versus transdermal menopausal hormone treatments on self-reported sleep domains and their association with vasomotor symptoms in recently menopausal women enrolled in the Kronos Early Estrogen Prevention Study (KEEPS). Menopause. 2018;25:145–53.
5. Faubion SS, Sood R, Kapoor E. Genitourinary syndrome of menopause: management strategies for the clinician. Mayo Clin Proc. 2017;92:1842–9.

6. Gandhi J, Chen A, Dagur G, Suh Y, Smith N, Cali B, Khan SA. Genitourinary syndrome of menopause: an overview of clinical manifestations, pathophysiology, etiology, evaluation, and management. Am J Obstet Gynecol. 2016;215:704–11.
7. Gartlehner G, Patel SV, Feltner C, Weber RP, Long R, Mullican K, Boland E, Lux L, Viswanathan M. Hormone therapy for the primary prevention of chronic conditions in postmenopausal women: evidence report and systematic review for the US Preventive Services Task Force. JAMA. 2017;318:2234–49.
8. Schiff I. Menopause. In: Kistner RW, editor. Gynecology: principles and practice. 7th ed. Chicago: Year Book Medical Pub; 1999.
9. Effects of hormone replacement therapy on endometrial histology in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. The Writing Group for the PEPI Trial. JAMA. 1996;275:370–75.
10. Ferenczy A, Gelfand MM. Endometrial histology and bleeding patterns in post-menopausal women taking sequential, combined estradiol and dydrogesterone. Maturitas. 1997;26:219–26.
11. Gomes AM, Baracat EC, Simões MJ, Haidar MA, Focchi GR, Evêncio-Neto J, de Lima GR. Morphologic and morphometric aspects of the endometrium of postmenopausal women before and after cyclic oestrogen replacement treatment. Eur J Obstet Gynecol Reprod Biol. 1997;74:79–82.
12. Deligdisch L. Hormonal pathology of the endometrium. Mod Pathol. 2000;13:285–94.
13. Grady D, Rubin SM, Petitti DB, Fox CS, Black D, Ettinger B, Ernster VL, Cummings SR. Hormone therapy to prevent disease and prolong life in postmenopausal women. Ann Intern Med. 1992;117:1016–37.
14. Whitehead MI, Fraser D. The effects of estrogens and progestogens on the endometrium. Modern approach to treatment. Obstet Gynecol Clin N Am. 1987;14:299–320.
15. Furness S, Roberts H, Marjoribanks J, Lethaby A. Hormone therapy in postmenopausal women and risk of endometrial hyperplasia. Cochrane Database Syst Rev. 2012;8:CD000402.
16. Grady D, Gebretsadik T, Kerlikowske K, Ernster V, Petitti D. Hormone replacement therapy and endometrial cancer risk: a meta-analysis. Obstet Gynecol. 1995;85:304–13.
17. Sjögren LL, Mørch LS, Løkkegaard E. Hormone replacement therapy and the risk of endometrial cancer: a systematic review. Maturitas. 2016;91:25–35.
18. Steinauer J, Autry AM. Extended cycle combined hormonal contraception. Obstet Gynecol Clin N Am. 2007;34:43–55, viii.
19. Allais G, Chiarle G, Sinigaglia S, Benedetto C. Menstrual migraine: a review of current and developing pharmacotherapies for women. Expert Opin Pharmacother. 2018;19:123–36.
20. van Zuuren EJ, Fedorowicz Z, Carter B, Pandis N. Interventions for hirsutism (excluding laser and photoepilation therapy alone). Cochrane Database Syst Rev. 2015;4:CD010334.
21. Arowojolu AO, Gallo MF, Lopez LM, Grimes DA. Combined oral contraceptive pills for treatment of acne. Cochrane Database Syst Rev. 2012;6:CD004425.
22. Iversen L, Sivasubramaniam S, Lee AJ, Fielding S, Hannaford PC: Lifetime cancer risk and combined oral contraceptives: the Royal College of General Practitioners' Oral Contraception Study. Am J Obstet Gynecol. 2017;216:580.e1–9.
23. Chiaffarino F, Parazzini F, La Vecchia C, Marsico S, Surace M, Ricci E. Use of oral contraceptives and uterine fibroids: results from a case-control study. Br J Obstet Gynaecol. 1999;106:857–60.
24. Ober WB. Effects of oral and intrauterine administration of contraceptives on the uterus. Hum Pathol. 1977;8:513–27.
25. Dallenbach-Hellweg G. Histopathology of the endometrium. 4th ed. New York: Springer; 1987.
26. Deligdisch L. Effects of hormone therapy on the endometrium. Mod Pathol. 1993;6:94–106.
27. Raymond EG, Lovely LP, Chen-Mok M, Seppälä M, Kurman RJ, Lessey BA. Effect of the Yuzpe regimen of emergency contraception on markers of endometrial receptivity. Hum Reprod. 2000;15:2351–5.
28. Swahn ML, Westlund P, Johannisson E, Bygdeman M. Effect of post-coital contraceptive methods on the endometrium and the menstrual cycle. Acta Obstet Gynecol Scand. 1996;75:738–44.
29. Marions L, Hultenby K, Lindell I, Sun X, Ståbi B, Gemzell Danielsson K. Emergency contraception with mifepristone and levonorgestrel: mechanism of action. Obstet Gynecol. 2002;100:65–71.
30. Vargas MF, Tapia-Pizarro AA, Henríquez SP, Quezada M, Salvatierra AM, Noe G, Munroe DJ, Velasquez LA, Croxatto HB. Effect of single post-ovulatory administration of levonorgestrel on gene expression profile during the receptive period of the human endometrium. J Mol Endocrinol. 2012;48:25–36.
31. Gemzell-Danielsson K, Berger C. P G L L: emergency contraception – mechanisms of action. Contraception. 2013;87:300–8.
32. Mentrikoski MJ, Shah AA, Hanley KZ, Atkins KA. Assessing endometrial hyperplasia and carcinoma treated with progestin therapy. Am J Clin Pathol. 2012;138:524–34.
33. Miranda MC, Mazur MT. Endometrial squamous metaplasia. An unusual response to progestin therapy of hyperplasia. Arch Pathol Lab Med. 1995;119:458–60.
34. Dockerty MB, Smith RA, Symmonds RE. Pseudomalignant endometrial changes induced by administration of new synthetic progestins. Proc Staff Meet Mayo Clin. 1959;34:321–8.
35. Cruz-Aquino M, Shenker L, Blaustein A. Pseudosarcoma of the endometrium. Obstet Gynecol. 1967;29:93–6.
36. Clement PB, Scully RE. Idiopathic postmenopausal decidual reaction of the endometrium. A clinico-

pathologic analysis of four cases. Int J Gynecol Pathol. 1988;7:152–61.
37. Iezzoni JC, Mills SE. Nonneoplastic endometrial signet-ring cells. Vacuolated decidual cells and stromal histiocytes mimicking adenocarcinoma. Am J Clin Pathol. 2001;115:249–55.
38. Critchley HO, Wang H, Jones RL, Kelly RW, Drudy TA, Gebbie AE, Buckley CH, McNeilly AS, Glasier AF. Morphological and functional features of endometrial decidualization following long-term intrauterine levonorgestrel delivery. Hum Reprod. 1998;13:1218–24.
39. Bernardini L, Araujo FE, Balmaceda JP. A case of permanent endometrial hypotrophy after long-term use of oral contraceptives. Hum Reprod. 1993;8:543–6.
40. Taylor HS, Ohleth K. Using bazedoxifene plus conjugated estrogens for treating postmenopausal women: a comprehensive review. Menopause. 2012;19:479–85.
41. The NAMS. Hormone therapy position statement advisory panel: the 2017 hormone therapy position statement of The North American Menopause Society. Menopause. 2017;2017(24):728–53.
42. Lello S, Capozzi A, Scambia G. The tissue-selective estrogen complex (bazedoxifene/conjugated estrogens) for the treatment of menopause. Int J Endocrinol. 2017;2017:5064725.
43. Gelfand MM, Ferenczy A. A prospective 1-year study of estrogen and progestin in postmenopausal women: effects on the endometrium. Obstet Gynecol. 1989;74:398–402.
44. Ryntz T, Lobo RA. Abnormal uterine bleeding. In: Lobo RA, Gershenson DM, Lentz GM, Valea FA, editors. Comprehensive gynecology. 7th ed. Philadelphia: Elsevier; 2017. p. 621–33.
45. Feeley KM, Wells M. Hormone replacement therapy and the endometrium. J Clin Pathol. 2001;54:435–40.
46. Byrjalsen I, Thormann L, Meinecke B, Riis BJ, Christiansen C. Sequential estrogen and progestogen therapy: assessment of progestational effects on the postmenopausal endometrium. Obstet Gynecol. 1992;79:523–8.
47. Carranza-Lira S, Martínez-Chéquer JC, Santa Rita MT, Ortiz de la Peña A, Pérez Y, Fernández RL. Endometrial changes according to hormone replacement therapy schedule. Menopause. 1998;5:86–9.
48. Habiba MA, Bell SC, Al-Azzawi F. Endometrial responses to hormone replacement therapy: histological features compared with those of late luteal phase endometrium. Hum Reprod. 1998;13:1674–82.
49. Magos AL, Brincat M, Studd JW, Wardle P, Schlesinger P, O'Dowd T. Amenorrhea and endometrial atrophy with continuous oral estrogen and progestogen therapy in postmenopausal women. Obstet Gynecol. 1985;65:496–9.
50. Hillard TC, Siddle NC, Whitehead MI, Fraser DI, Pryse-Davies J. Continuous combined conjugated equine estrogen-progestogen therapy: effects of medroxyprogesterone acetate and norethindrone acetate on bleeding patterns and endometrial histologic diagnosis. Am J Obstet Gynecol. 1992;167:1–7.
51. Piegsa K, Calder A, Davis JA, McKay-Hart D, Wells M, Bryden F. Endometrial status in post-menopausal women on long-term continuous combined hormone replacement therapy (Kliofem). A comparative study of endometrial biopsy, outpatient hysteroscopy and transvaginal ultrasound. Eur J Obstet Gynecol Reprod Biol. 1997;72:175–80.
52. Sturdee DW. Endometrial morphology and bleeding patterns as a function of progestogen supplementation. Int J Fertil Menopausal Stud. 1996;41:22–8.
53. Udoff L, Langenberg P, Adashi EY. Combined continuous hormone replacement therapy: a critical review. Obstet Gynecol. 1995;86:306–16.
54. Fernández-Murga L, Hermenegildo C, Tarín JJ, García-Pérez M-Á, Cano A. Endometrial response to concurrent treatment with vaginal progesterone and transdermal estradiol. Climacteric. 2012;15:455–9.
55. Moyer DL, de Lignieres B, Driguez P, Pez JP. Prevention of endometrial hyperplasia by progesterone during long-term estradiol replacement: influence of bleeding pattern and secretory changes. Fertil Steril. 1993;59:992–7.
56. Bjarnason K, Cerin A, Lindgren R, Weber T. Adverse endometrial effects during long cycle hormone replacement therapy. Scandinavian Long Cycle Study Group. Maturitas. 1999;32:161–70.
57. Sturdee DW, Ulrich LG, Barlow DH, Wells M, Campbell MJ, Vessey MP, Nielsen B, Anderson MC, Bragg AJ. The endometrial response to sequential and continuous combined oestrogen-progestogen replacement therapy. BJOG. 2000;107:1392–400.
58. Elliott J, Connor ME, Lashen H. The value of outpatient hysteroscopy in diagnosing endometrial pathology in postmenopausal women with and without hormone replacement therapy. Acta Obstet Gynecol Scand. 2003;82:1112–9.
59. Omodei U, Ferrazzi E, Ramazzotto F, Becorpi A, Grimaldi E, Scarselli G, Spagnolo D, Spagnolo L, Torri W. Endometrial evaluation with transvaginal ultrasound during hormone therapy: a prospective multicenter study. Fertil Steril. 2004;81:1632–7.
60. Heikkinen J, Vaheri R, Kainulainen P, Timonen U. Long-term continuous combined hormone replacement therapy in the prevention of postmenopausal bone loss: a comparison of high- and low-dose estrogen-progestin regimens. Osteoporos Int. 2000;11:929–37.
61. Nand SL, Webster MA, Baber R, O'Connor V. Bleeding pattern and endometrial changes during continuous combined hormone replacement therapy. The Ogen/Provera Study Group. Obstet Gynecol. 1998;91:678–84.
62. Oosterbaan HP, van Buuren AH, Schram JH, van Kempen PJ, Ubachs JM, van Leusden HA, Beyer GP. The effects of continuous combined transdermal oestrogen-progestogen treatment on bleeding

patterns and the endometrium in postmenopausal women. Maturitas. 1995;21:211–9.
63. Varila E, Wahlström T, Rauramo I. A 5-year follow-up study on the use of a levonorgestrel intrauterine system in women receiving hormone replacement therapy. Fertil Steril. 2001;76:969–73.
64. Kurman RJ, Félix JC, Archer DF, Nanavati N, Arce J, Moyer DL. Norethindrone acetate and estradiol-induced endometrial hyperplasia. Obstet Gynecol. 2000;96:373–9.
65. Te Linde RW, Henriksen E. Decidua like changes in the endometrium without pregnancy. Am J Obstet Gynecol. 1940;39:733–49.
66. Dallenbach-Hellweg G, Hohagen F. On the problem of premature decidualization induced by the embryo transfer. Lab Investig. 1985;52:17A.
67. Tamada T, Okagaki T, Maruyama M, Matsumoto S. Endometrial histology associated with an intrauterine contraceptive device. Am J Obstet Gynecol. 1967;98:811–7.
68. Bonney WA, Glasser SR, Clewe TH, Noyes RW, Cooper CL. Endometrial response to the intrauterine device. Am J Obstet Gynecol. 1966;96:101–13.
69. Mutter GL, Bergeron C, Deligdisch L, Ferenczy A, Glant M, Merino M, Williams ARW, Blithe DL. The spectrum of endometrial pathology induced by progesterone receptor modulators. Mod Pathol. 2008;21:591–8.
70. Williams ARW, Bergeron C, Barlow DH, Ferenczy A. Endometrial morphology after treatment of uterine fibroids with the selective progesterone receptor modulator, ulipristal acetate. Int J Gynecol Pathol. 2012;31:556–69.
71. Nogales FF, Crespo-Lora V, Cruz-Viruel N, Chamorro-Santos C, Bergeron C. Endometrial changes in surgical specimens of perimenopausal patients treated with ulipristal acetate for uterine leiomyomas. Int J Gynecol Pathol. 2017 Sep 13. doi: 10.1097/PGP.0000000000000450. [Epub ahead of print].
72. Donnez J, Donnez O, Matule D, Ahrendt H-J, Hudecek R, Zatik J, Kasilovskiene Z, Dumitrascu MC, Fernandez H, Barlow DH, Bouchard P, Fauser BCJM, Bestel E, Loumaye E. Long-term medical management of uterine fibroids with ulipristal acetate. Fertil Steril. 2016;105:165–73.e4.
73. Vosse M, Renard F, Coibion M, Neven P, Nogaret JM, Hertens D. Endometrial disorders in 406 breast cancer patients on tamoxifen: the case for less intensive monitoring. Eur J Obstet Gynecol Reprod Biol. 2002;101:58–63.
74. Goldstein SR. The effect of SERMs on the endometrium. Ann N Y Acad Sci. 2001;949:237–42.
75. Cohen I, Altaras MM, Shapira J, Tepper R, Rosen DJ, Cordoba M, Zalel Y, Figer A, Yigael D, Beyth Y. Time-dependent effect of tamoxifen therapy on endometrial pathology in asymptomatic postmenopausal breast cancer patients. Int J Gynecol Pathol. 1996;15:152–7.
76. Leslie KK, Walter SA, Torkko K, Stephens JK, Thompson C, Singh M. Effect of tamoxifen on endometrial histology, hormone receptors, and cervical cytology: a prospective study with follow-up. Appl Immunohistochem Mol Morphol. 2007;15:284–93.
77. López DML, Fernández YG, Sánchez AV, Alvarez MI, Reynaldo MIL, Delgado RC. Baseline hysteroscopic assessment of endometrium in asymptomatic postmenopausal women with estrogen receptor-positive breast cancer. Menopause. 2013;20:64–71.
78. Lubián López DM, Orihuela López F, García-Berbel Molina L, Boza Novo P, Pozuelo Solís E, Menor Almagro D, Comino Delgado R. Endometrial polyps in obese asymptomatic pre and postmenopausal patients with breast cancer: is screening necessary? Gynecol Oncol. 2014;133:56–62.
79. Bissett D, Davis JA, George WD. Gynaecological monitoring during tamoxifen therapy. Lancet. 1994;344:1244.
80. Committee Opinion No. 601. Tamoxifen and uterine cancer. Obstet Gynecol. 2014;123:1394–7.
81. Bertelli G, Valenzano M, Costantini S, Rissone R, Angiolini C, Signorini A, Gustavino C. Limited value of sonohysterography for endometrial screening in asymptomatic, postmenopausal patients treated with tamoxifen. Gynecol Oncol. 2000;78:275–7.
82. Cohen I, Perel E, Flex D, Tepper R, Altaras MM, Cordoba M, Beyth Y. Endometrial pathology in postmenopausal tamoxifen treatment: comparison between gynaecologically symptomatic and asymptomatic breast cancer patients. J Clin Pathol. 1999;52:278–82.
83. Marchesoni D, Driul L, Fabiani G, Di Loreto C, Cataldi P, Mozzanega B. Endometrial histologic changes in post-menopausal breast cancer patients using tamoxifen. Int J Gynaecol Obstet. 2001;75:257–62.
84. Seoud M, Shamseddine A, Khalil A, Salem Z, Saghir N, Bikhazi K, Bitar N, Azar G, Kaspar H. Tamoxifen and endometrial pathologies: a prospective study. Gynecol Oncol. 1999;75:15–9.
85. Ozşener S, Ozaran A, Itil I, Dikmen Y. Endometrial pathology of 104 postmenopausal breast cancer patients treated with tamoxifen. Eur J Gynaecol Oncol. 1998;19:580–3.
86. LE Donne M, Alibrandi A, Ciancimino L, Azzerboni A, Chiofalo B, Triolo O. Endometrial pathology in breast cancer patients: effect of different treatments on ultrasonographic, hysteroscopic and histological findings. Oncol Lett. 2013;5:1305–10.
87. Cohen I, Figer A, Altaras MM, Tepper R, Shapira J, Cordoba M, Yigael D, Arbel Y, Beyth Y. Common endometrial decidual reaction in postmenopausal breast cancer patients treated with tamoxifen and progestogens. Int J Gynecol Pathol. 1996;15:17–22.
88. Cohen I, Shapira J, Altaras M, Cordoba M, Rosen D, Beyth Y. Endometrial decidual changes in a postmenopausal woman treated with tamoxi-

fen and megestrol acetate. Br J Obstet Gynaecol. 1992;99:773–4.
89. Andersson M, Storm HH, Mouridsen HT. Incidence of new primary cancers after adjuvant tamoxifen therapy and radiotherapy for early breast cancer. J Natl Cancer Inst. 1991;83:1013–7.
90. Segna RA, Dottino PR, Deligdisch L, Cohen CJ. Tamoxifen and endometrial cancer. Mt Sinai J Med. 1992;59:416–8.
91. Magriples U, Naftolin F, Schwartz PE, Carcangiu ML. High-grade endometrial carcinoma in tamoxifen-treated breast cancer patients. J Clin Oncol. 1993;11:485–90.
92. Gusberg SB. Tamoxifen for breast cancer: associated endometrial cancer. Cancer. 1990;65:1463–4.
93. Fornander T, Rutqvist LE, Cedermark B, Glas U, Mattsson A, Silfverswärd C, Skoog L, Somell A, Theve T, Wilking N. Adjuvant tamoxifen in early breast cancer: occurrence of new primary cancers. Lancet. 1989;1:117–20.
94. Seoud MA, Johnson J, Weed JC. Gynecologic tumors in tamoxifen-treated women with breast cancer. Obstet Gynecol. 1993;82:165–9.
95. Carcangiu ML. Uterine pathology in tamoxifen-treated patients with breast cancer. Anat Pathol. 1997;2:53–70.
96. Braithwaite RS, Chlebowski RT, Lau J, George S, Hess R, Col NF. Meta-analysis of vascular and neoplastic events associated with tamoxifen. J Gen Intern Med. 2003;18:937–47.
97. Fisher B, Costantino JP, Redmond CK, Fisher ER, Wickerham DL, Cronin WM. Endometrial cancer in tamoxifen-treated breast cancer patients: findings from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14. J Natl Cancer Inst. 1994;86:527–37.
98. Davies C, Pan H, Godwin J, Gray R, Arriagada R, Raina V, et al. Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) Collaborative Group: long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. Lancet. 2013;381:805–16.
99. Dallenbach-Hellweg G, Schmidt D, Hellberg P, Bourne T, Kreuzwieser E, Dören M, Rydh W, Rudenstam G, Granberg S. The endometrium in breast cancer patients on tamoxifen. Arch Gynecol Obstet. 2000;263:170–7.
100. Deligdisch L, Kalir T, Cohen CJ, de Latour M, Le Bouedec G, Penault-Llorca F. Endometrial histopathology in 700 patients treated with tamoxifen for breast cancer. Gynecol Oncol. 2000;78:181–6.
101. Bland AE, Calingaert B, Secord AA, Lee PS, Valea FA, Berchuck A, Soper JT, Havrilesky L. Relationship between tamoxifen use and high risk endometrial cancer histologic types. Gynecol Oncol. 2009;112:150–4.
102. Cohen I, Azaria R, Fishman A, Tepper R, Shapira J, Beyth Y. Endometrial cancers in postmenopausal breast cancer patients with tamoxifen treatment. Int J Gynecol Pathol. 1999;18:304–9.
103. Barakat RR, Wong G, Curtin JP, Vlamis V, Hoskins WJ. Tamoxifen use in breast cancer patients who subsequently develop corpus cancer is not associated with a higher incidence of adverse histologic features. Gynecol Oncol. 1994;55:164–8.
104. Fisher B, Costantino JP, Wickerham DL, Redmond CK, Kavanah M, Cronin WM, Vogel V, Robidoux A, Dimitrov N, Atkins J, Daly M, Wieand S, Tan-Chiu E, Ford L, Wolmark N. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst. 1998;90:1371–88.
105. Wright JD, Desai VB, Chen L, Burke WM, Tergas AI, Hou JY, Accordino M, Ananth CV, Neugut AI, Hershman DL. Utilization of gynecologic services in women with breast cancer receiving hormonal therapy. Am J Obstet Gynecol. 2017;217:59.e1–12.
106. Wickerham DL, Fisher B, Wolmark N, Bryant J, Costantino J, Bernstein L, Runowicz CD. Association of tamoxifen and uterine sarcoma. J Clin Oncol. 2002;20:2758–60.
107. Clement PB, Oliva E. Young RH: üü adenosarcoma of the uterine corpus associated with tamoxifen therapy: a report of six cases and a review of tamoxifen-associated endometrial lesions. Int J Gynecol Pathol. 1996;15:222–9.
108. McCluggage WG, Abdulkader M, Price JH, Kelehan P, Hamilton S, Beattie J, Al-Nafussi A. Uterine carcinosarcomas in patients receiving tamoxifen. A report of 19 cases. Int J Gynecol Cancer. 2000;10:280–4.
109. Swerdlow AJ, Jones ME. British Tamoxifen Second Cancer Study Group: Tamoxifen treatment for breast cancer and risk of endometrial cancer: a case-control study. J Natl Cancer Inst. 2005;97:375–84.
110. Matsuo K, Ross MS, Bush SH, Yunokawa M, Blake EA, Takano T, Ueda Y, Baba T, Satoh S, Shida M, Ikeda Y, Adachi S, Yokoyama T, Takekuma M, Takeuchi S, Nishimura M, Iwasaki K, Yanai S, Klobocista MM, Johnson MS, Machida H, Hasegawa K, Miyake TM, Nagano T, Pejovic T, Shahzad MM, Im DD, Omatsu K, Ueland FR, Kelley JL, Roman LD. Tumor characteristics and survival outcomes of women with tamoxifen-related uterine carcinosarcoma. Gynecol Oncol. 2017;144:329–35.
111. Nuovo MA, Nuovo GJ, McCaffrey RM, Levine RU, Barron B, Winkler B. Endometrial polyps in postmenopausal patients receiving tamoxifen. Int J Gynecol Pathol. 1989;8:125–31.
112. Corley D, Rowe J, Curtis MT, Hogan WM, Noumoff JS, Livolsi VA. Postmenopausal bleeding from unusual endometrial polyps in women on chronic tamoxifen therapy. Obstet Gynecol. 1992;79:111–6.
113. Lahti E, Blanco G, Kauppila A, Apaja-Sarkkinen M, Taskinen PJ, Laatikainen T. Endometrial changes

in postmenopausal breast cancer patients receiving tamoxifen. Obstet Gynecol. 1993;81:660–4.
114. Kennedy MM, Baigrie CF, Manek S. Tamoxifen and the endometrium: review of 102 cases and comparison with HRT-related and non-HRT-related endometrial pathology. Int J Gynecol Pathol. 1999;18:130–7.
115. Cohen I, Azaria R, Bernheim J, Shapira J, Beyth Y. Risk factors of endometrial polyps resected from postmenopausal patients with breast carcinoma treated with tamoxifen. Cancer. 2001;92:1151–5.
116. Liedman R, Lindahl B, Andolf E, Willen R, Ingvar C, Ranstam J. Disaccordance between estimation of endometrial thickness as measured by transvaginal ultrasound compared with hysteroscopy and directed biopsy in breast cancer patients treated with tamoxifen. Anticancer Res. 2000;20:4889–91.
117. Sasaki LMP, Andrade KRC, Figueiredo ACMG, Wanderley MDS, Pereira MG. Factors associated with malignancy in hysteroscopically resected endometrial polyps: a systematic review and meta-analysis. J Minim Invasive Gynecol. 2018;25:1–9.
118. Schlesinger C, Kamoi S, Ascher SM, Kendell M, Lage JM, Silverberg SG. Endometrial polyps: a comparison study of patients receiving tamoxifen with two control groups. Int J Gynecol Pathol. 1998;17:302–11.
119. Biron-Shental T, Tepper R, Fishman A, Shapira J, Cohen I. Recurrent endometrial polyps in postmenopausal breast cancer patients on tamoxifen. Gynecol Oncol. 2003;90:382–6.
120. Di Benedetto L, Giovanale V, Caserta D. Endometrial tubal metaplasia in a young puerperal woman after breast cancer. Int J Clin Exp Pathol. 2015;8:7610–3.
121. Cohen I, Bernheim J, Azaria R, Tepper R, Sharony R, Beyth Y. Malignant endometrial polyps in postmenopausal breast cancer tamoxifen-treated patients. Gynecol Oncol. 1999;75:136–41.
122. McCluggage WG, Sumathi VP, McManus DT. Uterine serous carcinoma and endometrial intraepithelial carcinoma arising in endometrial polyps: report of 5 cases, including 2 associated with tamoxifen therapy. Hum Pathol. 2003;34:939–43.
123. Dominick S, Hickey M, Chin J, Su HI. Levonorgestrel intrauterine system for endometrial protection in women with breast cancer on adjuvant tamoxifen. Cochrane Database Syst Rev. 2015;12:CD007245.
124. Cummings SR, Eckert S, Krueger KA, Grady D, Powles TJ, Cauley JA, Norton L, Nickelsen T, Bjarnason NH, Morrow M, Lippman ME, Black D, Glusman JE, Costa A, Jordan VC. The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial. Multiple Outcomes of Raloxifene Evaluation. JAMA. 1999;281:2189–97.
125. Goldstein SR. Update on raloxifene to prevent endometrial-breast cancer. Eur J Cancer. 2000;36(Suppl 4):S54–6.
126. Martino S, Disch D, Dowsett SA, Keech CA, Mershon JL. Safety assessment of raloxifene over eight years in a clinical trial setting. Curr Med Res Opin. 2005;21:1441–52.
127. Boss SM, Huster WJ, Neild JA, Glant MD, Eisenhut CC, Draper MW. Effects of raloxifene hydrochloride on the endometrium of postmenopausal women. Am J Obstet Gynecol. 1997;177:1458–64.
128. Davies GC, Huster WJ, Shen W, Mitlak B, Plouffe L, Shah A, Cohen FJ. Endometrial response to raloxifene compared with placebo, cyclical hormone replacement therapy, and unopposed estrogen in postmenopausal women. Menopause. 1999;6:188–95.
129. Delmas PD, Bjarnason NH, Mitlak BH, Ravoux AC, Shah AS, Huster WJ, Draper M, Christiansen C. Effects of raloxifene on bone mineral density, serum cholesterol concentrations, and uterine endometrium in postmenopausal women. N Engl J Med. 1997;337:1641–7.
130. Goldstein SR, Scheele WH, Rajagopalan SK, Wilkie JL, Walsh BW, Parsons AK. A 12-month comparative study of raloxifene, estrogen, and placebo on the postmenopausal endometrium. Obstet Gynecol. 2000;95:95–103.
131. DeMichele A, Troxel AB, Berlin JA, Weber AL, Bunin GR, Turzo E, Schinnar R, Burgh D, Berlin M, Rubin SC, Rebbeck TR, Strom BL. Impact of raloxifene or tamoxifen use on endometrial cancer risk: a population-based case-control study. J Clin Oncol. 2008;26:4151–9.
132. Benda JA. Clomiphene's effect on endometrium in infertility. Int J Gynecol Pathol. 1992;11:273–82.
133. Birkenfeld A, Navot D, Levij IS, Laufer N, Beier-Hellwig K, Goecke C, Schenker JG, Beier HM. Advanced secretory changes in the proliferative human endometrial epithelium following clomiphene citrate treatment. Fertil Steril. 1986;45:462–8.
134. Thatcher SS, Donachie KM, Glasier A, Hillier SG, Baird DT. The effects of clomiphene citrate on the histology of human endometrium in regularly cycling women undergoing in vitro fertilization. Fertil Steril. 1988;49:296–301.
135. Li TC, Warren MA, Murphy C, Sargeant S, Cooke ID. A prospective, randomised, cross-over study comparing the effects of clomiphene citrate and cyclofenil on endometrial morphology in the luteal phase of normal, fertile women. Br J Obstet Gynaecol. 1992;99:1008–13.
136. Triwitayakorn A, Suwajanakorn S, Triratanachat S, Sampatanukul P, Pruksananonda K, Sereepapong W. Effects of initiation day of clomiphene citrate on the endometrium of women with regular menstrual cycles. Fertil Steril. 2002;78:102–7.
137. Floyd WS. Danazol: endocrine and endometrial effects. Int J Fertil. 1980;25:75–80.
138. Fedele L, Marchini M, Bianchi S, Baglioni A, Bocciolone L, Nava S. Endometrial patterns during danazol and buserelin therapy for endometriosis: comparative structural and ultrastructural study. Obstet Gynecol. 1990;76:79–84.
139. Beaumont H, Augood C, Duckitt K, Lethaby A. Danazol for heavy menstrual bleeding. Cochrane Database Syst Rev. 2007;3:CD001017.

140. Robins JC. Therapies for the treatment of abnormal uterine bleeding. Curr Womens Health Rep. 2001;1:196–201.
141. Tan YH, Lethaby A. Pre-operative endometrial thinning agents before endometrial destruction for heavy menstrual bleeding. Cochrane Database Syst Rev. 2013;11:CD001124.
142. Bradley LD, Gueye N-A. The medical management of abnormal uterine bleeding in reproductive-aged women. Am J Obstet Gynecol. 2016;214:31–44.
143. Soh E, Sato K. Clinical effects of danazol on endometrial hyperplasia in menopausal and postmenopausal women. Cancer. 1990;66:983–8.
144. Tamaoka Y, Orikasa H, Sumi Y, Sakakura K, Kamei K, Nagatani M, Ezawa S. Direct effect of danazol on endometrial hyperplasia in adenomyotic women: treatment with danazol containing intrauterine device. Hum Cell. 2000;13:127–33.
145. Wentz AC, Jones GS, Sapp KC, King TM. Progestational activity of danazol in the human female subject. Am J Obstet Gynecol. 1976;126:378–84.
146. Marchini M, Fedele L, Bianchi S, Di Nola G, Nava S, Vercellini P. Endometrial patterns during therapy with danazol or gestrinone for endometriosis: structural and ultrastructural study. Hum Pathol. 1992;23:51–6.
147. Jeppsson S, Mellquist P, Rannevik G. Short-term effects of danazol on endometrial histology. Acta Obstet Gynecol Scand Suppl. 1984;123:41–4.
148. Fedele L, Bianchi S, Marchini M, Di Nola G. Histological impact of medical therapy – clinical implications. Br J Obstet Gynaecol. 1995;102(Suppl 12):8–11.
149. Brooks PG, Serden SP, Davos I. Hormonal inhibition of the endometrium for resectoscopic endometrial ablation. Am J Obstet Gynecol. 1991;164:1601–6; discussion 1606–1608.
150. Reshef E, Segars JH, Hill GA, Pridham DD, Yussman MA, Wentz AC. Endometrial inadequacy after treatment with human menopausal gonadotropin/human chorionic gonadotropin. Fertil Steril. 1990;54:1012–6.
151. Bonhoff A, Naether O, Johannisson E, Bohnet HG. Morphometric characteristics of endometrial biopsies after different types of ovarian stimulation for infertility treatment. Fertil Steril. 1993;59:560–6.
152. Campbell BF, Phipps WR, Nagel TC, Tagatz GE. Endometrial biopsies during treatment with subcutaneous pulsatile gonadotropin-releasing hormone and luteal-phase human chorionic gonadotropin. Int J Fertil. 1988;33:329–33.
153. Sterzik K, Dallenbach C, Schneider V, Sasse V, Dallenbach-Hellweg G. In vitro fertilization: the degree of endometrial insufficiency varies with the type of ovarian stimulation. Fertil Steril. 1988;50:457–62.
154. Garcia JE, Acosta AA, Hsiu JG, Jones HW. Advanced endometrial maturation after ovulation induction with human menopausal gonadotropin/human chorionic gonadotropin for in vitro fertilization. Fertil Steril. 1984;41:31–5.
155. Sharma V, Whitehead M, Mason B, Pryse-Davies J, Ryder T, Dowsett M, Campbell S, Collins W. Influence of superovulation on endometrial and embryonic development. Fertil Steril. 1990;53:822–9.
156. Child TJ, Gulekli B, Sylvestre C, Tan SL. Ultrasonographic assessment of endometrial receptivity at embryo transfer in an in vitro maturation of oocyte program. Fertil Steril. 2003;79:656–8.
157. Elizur SE, Son W-Y, Yap R, Gidoni Y, Levin D, Demirtas E, Tan S-L. Comparison of low-dose human menopausal gonadotropin and micronized 17beta-estradiol supplementation in in vitro maturation cycles with thin endometrial lining. Fertil Steril. 2009;92:907–12.
158. Casper RF. Clinical uses of gonadotropin-releasing hormone analogues. CMAJ. 1991;144:153–8.
159. Lethaby A, Puscasiu L, Vollenhoven B. Preoperative medical therapy before surgery for uterine fibroids. Cochrane Database Syst Rev. 2017;11:CD000547.
160. Lemay A, Jean C, Faure N. Endometrial histology during intermittent intranasal luteinizing hormone-releasing hormone (LH-RH) agonist sequentially combined with an oral progestogen as an antiovulatory contraceptive approach. Fertil Steril. 1987;48:775–82.
161. Spitz IM, Bardin CW. Mifepristone (RU 486)—a modulator of progestin and glucocorticoid action. N Engl J Med. 1993;329:404–12.
162. Johannisson E, Oberholzer M, Swahn ML, Bygdeman M. Vascular changes in the human endometrium following the administration of the progesterone antagonist RU 486. Contraception. 1989;39:103–17.
163. Swahn ML, Bygdeman M. The effect of the antiprogestin RU 486 on uterine contractility and sensitivity to prostaglandin and oxytocin. Br J Obstet Gynaecol. 1988;95:126–34.
164. Spitz IM. Mifepristone: where do we come from and where are we going? Clinical development over a quarter of a century. Contraception. 2010;82:442–52.
165. Croxatto HB, Kovács L, Massai R, Resch BA, Fuentealba B, Salvatierra AM, Croxatto HD, Zalányi S, Viski S, Krenács L. Effects of long-term low-dose mifepristone on reproductive function in women. Hum Reprod. 1998;13:793–8.
166. Croxatto HB, Salvatierra AM, Croxatto HD, Fuentealba B. Effects of continuous treatment with low dose mifepristone throughout one menstrual cycle. Hum Reprod. 1993;8:201–7.
167. Swahn ML, Bygdeman M, Cekan S, Xing S, Masironi B, Johannisson E. The effect of RU 486 administered during the early luteal phase on bleeding pattern, hormonal parameters and endometrium. Hum Reprod. 1990;5:402–8.
168. Li TC, Dockery P, Thomas P, Rogers AW, Lenton EA, Cooke ID. The effects of progesterone receptor blockade in the luteal phase of normal fertile women. Fertil Steril. 1988;50:732–42.

169. Batista MC, Cartledge TP, Zellmer AW, Merino MJ, Axiotis C, Loriaux DL, Nieman LK. Delayed endometrial maturation induced by daily administration of the antiprogestin RU 486: a potential new contraceptive strategy. Am J Obstet Gynecol. 1992;167:60–5.
170. Cameron ST, Critchley HO, Thong KJ, Buckley CH, Williams AR, Baird DT. Effects of daily low dose mifepristone on endometrial maturation and proliferation. Hum Reprod. 1996;11:2518–26.
171. Heikinheimo O, Hsiu JG, Gordon K, Kim S, Williams RF, Gibbons WE, Hodgen GD. Endometrial effects of RU486 in primates – antiproliferative action despite signs of estrogen action and increased cyclin-B expression. J Steroid Biochem Mol Biol. 1996;59:179–90.
172. Gemzell-Danielsson K, Westlund P, Johannisson E, Swahn ML, Bygdeman M, Seppälä M. Effect of low weekly doses of mifepristone on ovarian function and endometrial development. Hum Reprod. 1996;11:256–64.
173. Jimenez-Moreno V, Billeter M, Liu CQ, Gordon K, Mahony M. Local effects of mifepristone on the nonhuman primate endometrium. Fertil Steril. 2000;74:134–40.
174. Baird DT, Brown A, Critchley HOD, Williams AR, Lin S, Cheng L. Effect of long-term treatment with low-dose mifepristone on the endometrium. Hum Reprod. 2003;18:61–8.
175. Newfield RS, Spitz IM, Isacson C, New MI. Long-term mifepristone (RU486) therapy resulting in massive benign endometrial hyperplasia. Clin Endocrinol. 2001;54:399–404.
176. Eisinger SH, Meldrum S, Fiscella K, le Roux HD, Guzick DS. Low-dose mifepristone for uterine leiomyomata. Obstet Gynecol. 2003;101:243–50.
177. Horne FM, Blithe DL. Progesterone receptor modulators and the endometrium: changes and consequences. Hum Reprod Update. 2007;13:567–80.
178. Koering MJ, Healy DL, Hodgen GD. Morphologic response of endometrium to a progesterone receptor antagonist, RU486, in monkeys. Fertil Steril. 1986;45:280–7.
179. Wheeler DT, Bristow RE, Kurman RJ. Histologic alterations in endometrial hyperplasia and well-differentiated carcinoma treated with progestins. Am J Surg Pathol. 2007;31:988–98.
180. Parra-Herran C, Cesari M, Djordjevic B, Grondin K, Kinloch M, Köbel M, Pirzada A, Plotkin A, Gilks CB. Canadian consensus-based and evidence-based guidelines for benign endometrial pathology reporting in biopsy material. Int J Gynecol Pathol. 2018 Apr 19. doi:10.1097/PGP.0000000000000481. [Epub ahead of print].