Hormone Therapy Effects on the Uterus

Liane Deligdisch-Schor

1 General Considerations

The uterine tissue is exquisitely sensitive to hormonal influences, being able to translate them into functional and structural changes with promptitude and versatility. The complex interplay mediated by finely tuned feedback mechanisms between pituitary gland and gonadal functions, functionally related to the central nervous system, reaches its target in the uterine tissue securing the reproductive role of the uterus. Normal reproduction is based on the cyclic changes taking place in the entire female genital system and especially in the inner lining of the uterus, the endometrium. The programming of events in the endometrium, a highly differentiated and diversified tissue (glands, stroma, blood vessels), is regulated by the presence of receptors, essential to the transfers and translocation of the hormones secreted into the blood stream, and their translation into structural changes at the target tissue.

The most commonly involved gonad-secreted hormones are steroid hormones, estrogens and progesterone, bound to receptors, forming hormone-receptor complexes. The activated steroid receptor functions as a transcription factor modulating the synthesis of specific mRNA, responsible for the cellular action of the hormone. The receptor-bound hormone is transported into the cellular compartments, from replenishment in the cytoplasm to "shuttling" into nuclear chromatin-bound complexes which dispatch it to organelles by recruiting cell-specific signal-modifying proteins resulting in effects on cells such as proliferation, secretion, and apoptosis in normal cycles [1].

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The biologic activity of the steroid hormones is maintained only while the nuclear site is occupied by the hormone-receptor complex, thus duration of exposure, as well as concentration are related to effect. The absence or decrease of hormones results eventually in atrophic changes; the excess of hormones may produce irregular patterns of proliferation, hyperplasia, and neoplasia. Clinically, abnormal hormonal stimulation may be associated with infertility, abnormal vaginal bleeding (prolonged, irregular or reduced), often associated with benign lesions such as leiomyomas, adenomyosis, endometrial polyps, and uterine neoplasia, as well as a host of systemic disorders such as those encountered in peri- and post-menopausal syndromes.

Hormone therapy is used to counteract the deleterious effects of "natural", noniatrogenic, abnormal hormonal function. Hormone therapy is now widely prescribed, being used by millions of women all over the world. It seems that actually most women would use at least some hormone therapy at some point of their life. Adolescents and young women use oral contraceptives, sometime also prescribed during the perimenopausal years. Hormones are prescribed for irregular vaginal bleeding, uterine enlargement due to leiomyoma and adenomyosis, for symptoms due to hormone deprivation as in menopause or premature ovarian failure. Hormone therapy is used for infertility associated in numerous cases with hormonal inadequacy and reproductive technology includes ovulation stimulation by hormones. Postmenopausal symptoms are widely treated with hormones despite controversial data on their safety and efficiency; the regimens are shifting being almost permanently subjects for change. Hormone therapy is used for the adjuvant treatment of breast and uterine cancer, most frequently for reversal of endometrial hyperplasia. Tamoxifen, successfully used in breast cancer, is sometime associated with endometrial neoplasms, polyps, and endometrial carcinoma. Hormone therapy is also used for treatment of congenital abnormal sexual development and of gender dysphoria.

Hormone therapy elicits important changes in the physiopathology and structure of uterine tissues. These changes are difficult to be adequately and reliably described in textbooks because of the diversity of the histological, histochemical, and immunohistological patterns resulting from permanently changing therapeutic regimens, multiple and often controversial concepts, changing statistical data and identification of new cellular markers.

Uterine biopsies, mostly endometrial biopsies obtained by D&C or endometrial aspirates routinely used during or after hormone therapy in order to evaluate the effects on the endometrial tissue and occasionally on the myometrium and other pelvic structures, are often difficult to interpret. Confusion with premalignant and frankly neoplastic tissues, for example in estrogen-induced glandular hyperplasia with stromal breakdown, may occur. Underdiagnosis of an iatrogenically modified malignant tissue, such as decidualized stroma and secretory glands in endometrial neoplasm under progestin hormonal therapy, can be dangerously misleading.

The microscopic analysis of histologic changes in the uterine, especially endometrial tissue submitted to hormonal therapeutic manipulations, reveals the response or lack thereof to the administered, mostly, steroid hormones which is closely

related to the abundance and distribution pattern of receptors and other significant proteins. This is detectable by immunohistologic markers used in special stains of the sectioned tissue; molecular biology research demonstrates a permanent renewal of these markers.

It therefore appears that the uterus, an organ composed of tissues highly sensitive and receptive to hormones due to the abundance of receptors, is capable of profound and diverse structural changes with a wide variety of patterns on microscopic examination, resulting from physiological and pathological hormonal influences. The interpretation of these patterns becomes more complex and difficult as the administration of hormones is permanently changing regimens and dosages, and is modified by new products and new concepts.

The following histopathologic descriptions are describing the relevant changes of the uterus, especially of the endometrium, consistent with diagnostic categories, in most commonly used hormonal therapies.

2 Iatrogenic Hormonal Effects on the Uterus

2.1 Hormonal Contraceptive Therapy

The most commonly, effectively used contraceptive method is based on hormonal suppression of ovulation and increase of cervical mucus density. The first "pill" was marketed and approved for use in the United States in the early 1960s with the name of ENOVID. It was composed of both estrogen (ethynyl estradiol) and progesterone/progestin. Hormonal contraception was first administered sequentially as an attempt to imitate the natural menstrual cycle, first estrogen then progesterone. This method however turned out to be relatively unsafe, with occasional failures to prevent pregnancy, irregular vaginal bleeding, and some cases of endometrial hyperplasia and neoplasia [2, 3]. In 1970, sequential hormone contraception was suspended in the United States. Since then, the most commonly administered "pill" is the combined estrogen-progesterone and more recently the progesterone-only pill. The most common hormonal contraception is the oral contraception (OC). Hormonal contraception also includes subcutaneous "patches" implants, intravaginal rings, intrauterine devices, and injections, all based on long-lasting release of steroid hormones, mainly progesterone.

The ovulation suppression is based on the negative feedback of estrogen and progesterone on the gonadotropin-releasing hormone (GnRH) secreted by the anterior pituitary lobe under hypothalamic stimulation, with decrease of follicle-stimulating and luteinizing hormones (FSH and LH), resulting in follicle development inhibition and preventing the mid-cycle surge of LH with absent ovulation. Cervical mucus becomes less permeable for sperm, mostly due to the progesterone effect.

Combined OC are also used for noncontraceptive purposes, and also for the treatment of polycystic ovarian syndrome, hirsutism, menstrual disorders, and menorrhagia. The effect of hormonal contraceptives on the endometrium is related to dosage and potency of the hormones. High-dose high-potency OC, not any more used in the United States in recent years, produces marked stromal hyperplasia with decidual reaction, smooth muscle hyperplasia suggestive of neoplasia (pseudosarcoma), and glandular atrophy of the endometrial tissue (Fig. 1). Currently used regimens containing lower doses and lower potency produce an arrest of proliferation in the first cycles with straight or slightly coiled glands lined by immature epithelial cells with nuclei showing an evenly distributed chromatin network. The thick nuclear membrane, coarse chromatin clumps, and mitotic activity seen in natural cycling proliferative endometrium, are absent. The cytoplasm contains randomly distributed vacuoles, and the apical border, unlike that of natural secretory endometrium, is smooth and well defined (Fig. 2).

The endometrial microscopic appearance on biopsies from women taking hormonal contraceptives display a variety of changes related to the effect of the hormones taken, their strength, dosage, duration of treatment (Table 1). The age of the patient, metabolic disturbances such as obesity or diabetes, hyperestrogenic conditions like ovarian hyperthecosis, polycystic syndrome, endometriosis may influence the response to hormonal contraception. Locally in the uterine tissue, the amount and distribution of receptors is related to the changes of tissue architectural structure and of the individual cells.

The predominant effect of the combined OC pill on the endometrial target tissue is that of progesterone featuring an appearance somehow resembling the secretory postovulatory endometrium, however, with major differences. The normal, natural

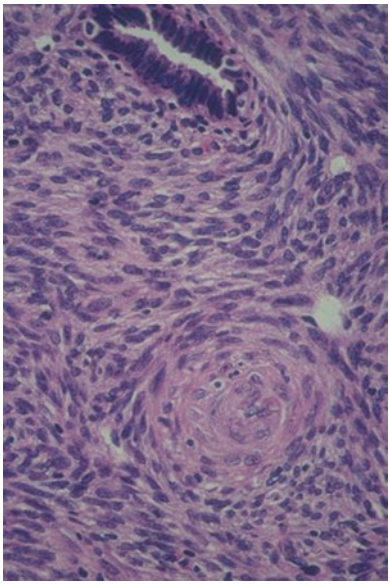

Fig. 1 Effect of high-potency OC: endometrial stromal and smooth muscle hyperplasia (pseudosarcoma), H&E ×100

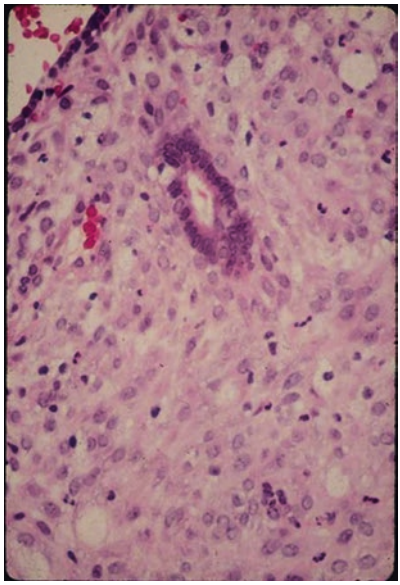

Fig. 2 OC effect on endometrium: inactive gland lined by immature cuboidal epithelial cells with scant abortive secretion in lumen and stromal decidual reaction with scattered leukocytes. H&E ×100

Table 1 Endometrial histology in oral contraceptive therapy

Predominant stroma over glands volume	
Glands	Arrest of epithelial proliferation
	Absent or abortive secretion
	Linear apical cell border
Stroma	Early edema
	Decidual reaction/ pseudopregnancy decidua
	Scattered leukocytes
Blood vessels	Absent spiral arterioles
	Venous sinusoidal dilation
Inactive or atrophic endometrium in prolonged OC therapy	

proportion of endometrial glandular versus stromal tissue is about 50/50%. With the predominantly progestational effect of hormonal contraceptives, the stroma becomes voluminous, and the glandular compartment is markedly reduced to an extent depending on the duration of the hormone administration (Fig. 3). The stroma is first edematous then gradually becomes decidualized with plump pavement-like cells with round nuclei and an abundant cytoplasm loaded with glucose, polymucosaccharides, proteins, and other nutrients destined for a possibly implanting blastocyst, as in natural endometrial cycles. However, the glands which are secretory in normal postovulatory cycles, with first subnuclear then supranuclear glycogen vacuoles, or as in later days of the cycle, "sawmill"-shaped with abundant secretion in the lumen, do not show these features with OC therapy: They appear rather inactive,

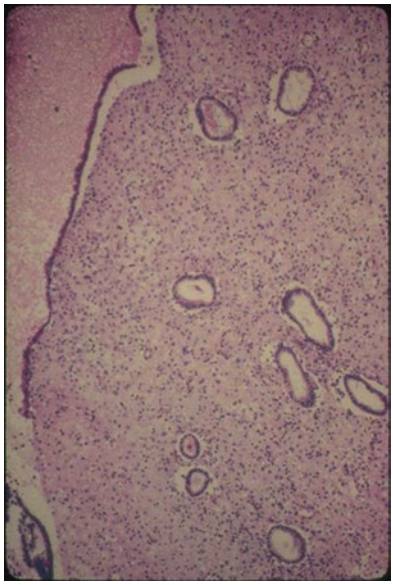

Fig. 3 OC effect on endometrium: stromal hyperplasia and rarefied inactive to atrophic glands. H&E ×40

small, tubular, straight, and lined by cuboidal or flat epithelial cells, with a straight luminal border and occasional droplets of secretion in their lumen (abortive secretion as in Fig. 2).

The blood vessels which in natural, functional cycles become thickened and coiled ("spiral arterioles") presenting an increased surface, therefore more chances for implantation for a possible fertilized ovum whose trophoblast is "searching" for spiral arterioles containing maternal blood, are thin and straight with OC therapy. Some blood vessels are abnormally dilated, containing blood clots. Superficial dilated venules and scattered lymphoid and polymorphonuclear leukocytes are present. Angiectasis and thrombosis are associated with breakthrough bleeding occurring sometime under progesterone-dominated contraceptive regimen.

The histologic appearance of the endometrium is not consistent with any physiological phase of the "dating" system used by pathologists to determine the adequacy of endometrial cyclic development for gestational purposes (Figs. 2 and 3). The endometrium treated with hormonal contraceptives is profoundly inadequate for implantation of a fertilized ovum, i.e., blastocyst; therefore, even if ovulation and fertilization took place, the decidualized endometrium, especially its compact surface will not permit implantation as it mimics pregnancy changes (pseudopregnancy endometrium). An already pregnant uterus cannot become pregnant! Experienced gynecologic pathologists recognize the "contraceptive endometrium" on the discrepancy between edematous (early-stage therapy) then decidualized (pseudogestational) and eventually thinned endometrial stroma and the inactive nonsecretory glands as well as the absence of spiral arterioles. The presence in the endometrial stroma of scattered leukocytes among decidual cells is an uncharacteristic finding for natural cycles in which numerous leukocytes infiltrate the stroma

shortly before the apoptotic changes of endometrial glandular epithelium and stroma during menstrual shedding. Prolonged use of hormonal contraceptive therapy may elicit a gradual atrophy of endometrial glands and thinning of the endometrial stroma with reduced decidual change. Also described in women taking OC is endocervical microglandular hyperplasia (Fig. 4) sometime with squamous metaplasia, similar to that seen in pregnancy.

The histologic patterns seen in endometrial biopsies from women receiving OC are unlike any "natural" noniatrogenic endometrial pattern, normal or pathologic. The combination of inactive glands, abortive secretion, and decidual stroma with thin blood vessels is characteristic of only OC therapy.

Progesterone receptor modulators (PRM), such as mifepristone, are used for contraception as well. Their effect on the endometrium appears to be mixed secretory, proliferative, and inactive glands with some cystic dilation [4]. The use of PRM as contraceptives is debatable and histological studies are limited; no malignant developments have been reported with this therapy.

2.2 Hormonal Therapy for Infertility

A large proportion of infertility cases are related to hormonal anomalies eliciting premature ovarian failure, anovulatory cycles, and/or amenorrhea. The most commonly employed method to "reactivate" the endometrial cyclic changes preparing the maternal tissue to host an implanting blastocyst is to stimulate the ovary to both ovulate and secrete steroid hormones that will elicit structural changes in the uterine

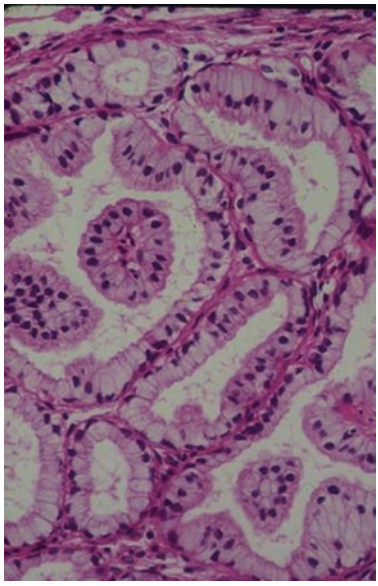

Fig. 4 Effect of OC: Endocervical gland hyperplasia. H&E ×100

target tissues, mainly the endometrium, and also in the myometrial tissue. The hormones that stimulate the ovary are chiefly gonadotropin-releasing hormones (GnRH) and their agonists, follicle-stimulating hormone (FSH), and luteinizing hormone (LH), to be secreted by the anterior lobe of the pituitary gland. Ovarian stimulation inhibits the negative feedback at the level of the thalamus and therefore stimulates the secretion of GnRH re-establishing the cyclic fertility-promoting hormonal activities of the uterus [1]. The response of the target tissues is variable but improves constantly, and successful pregnancies obtained with ovulation stimulation are numerous (see Chapter 2). Clomiphene citrate, a SERM, is frequently used, sometimes with associated steroid hormones. Multiple gestations are more common due to multiple ovulation as an ovarian stimulation effect; fortunately, overstimulation syndrome with occasional serious deleterious consequences, such as ovarian infarct and peritonitis, are presently very rare (Fig. 5).

The purpose of ovarian stimulation is the establishment of regular cyclic ovulation following normal follicle maturation and timely release of the ovule(s) at ovulation. The uterine tissues are prepared to serve as hosts to the implanting conceptus by modulating functions and structures adequately under the influences of estrogen and progesterone secreted cyclically by granulosa cells in the maturing, stimulated follicle and by the corpus luteum promptly after ovulation. The uterine target tissues are expected to respond adequately by normal proliferation and secretion, as in spontaneous normal cycles. Histologic studies of endometrial D&C tissue obtained in cases of subsequent failures concluded that no single finding seemed to be relevant for spontaneous pregnancy termination occurring in pregnancies which develop after iatrogenic ovulation stimulation [5]. The secretory changes in glands were observed to lag behind the secretory changes in the stroma, with subnuclear and supranuclear vacuoles in the glandular epithelium concomitant with decidual stro-

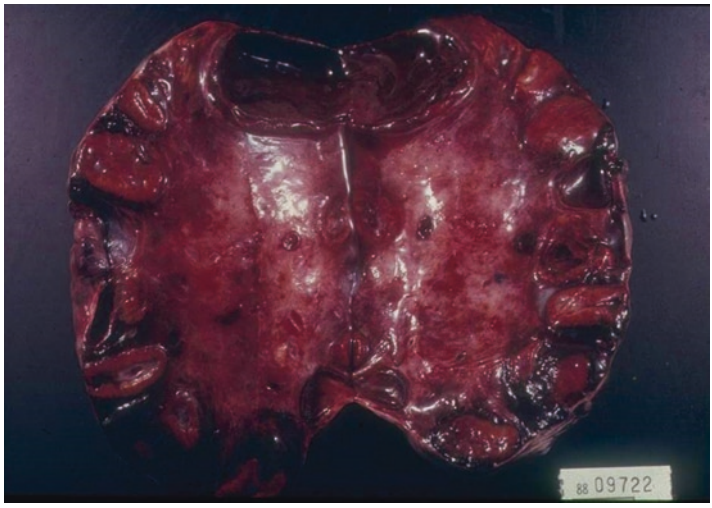

Fig. 5 Infarcted ovary due to iatrogenic hyperstimulation

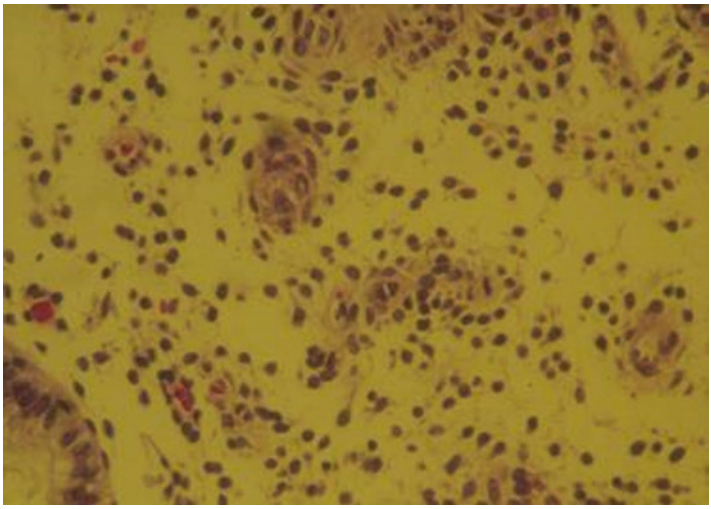

Fig. 6 Effect of ovulation stimulation: secretory endometrium with spiral arterioles surrounded by decidual reaction consistent with day 22–23. H&E ×40

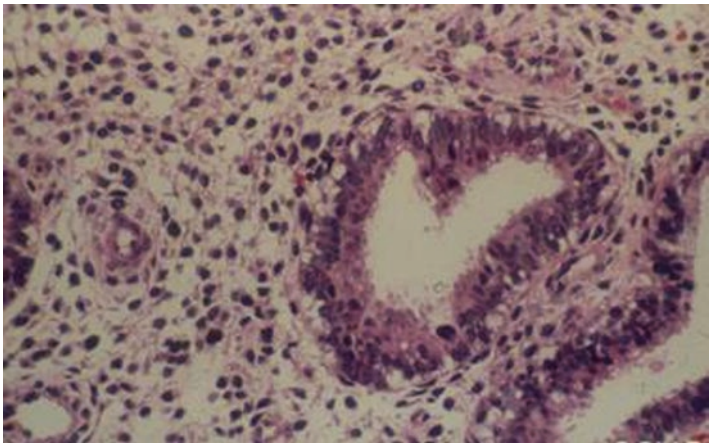

Fig. 7 Same endometrial biopsy: secretory glands with sub- and supranuclear vacuoles consistent with day 16–17. H&E ×100

mal reaction and spiral arterioles (Figs. 6 and 7). Mild inflammatory infiltrates can be present during early gestation possibly representing autoimmune endometritis [6].

An unusual serious complication occurred leading to a first trimester abortion in a patient after ovarian stimulation. The patient had a history of polycystic ovarian disease and endometrial glandular hyperplasia, and was treated with hormonal ovulation stimulation that resulted in a triplet gestation. She aborted at 9 weeks

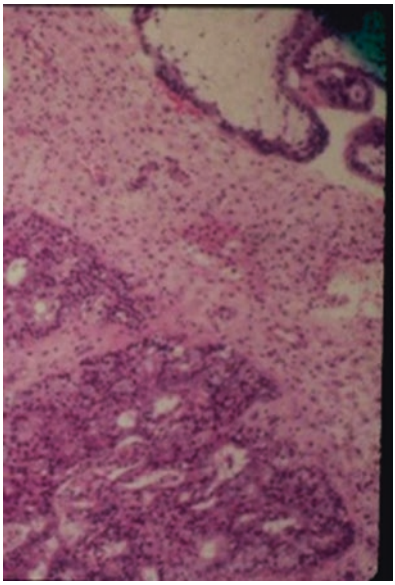

Fig. 8 Unusual "bedfellows" in endometrial biopsy: gestational and neoplastic changes of endometrium in aborted triplet pregnancy after ovulation stimulation of patient with previous polycystic ovarian disease and endometrial glandular hyperplasia. Chorionic villi (upper right corner), decidua, adenocarcinoma (lower left corner). H&E ×40

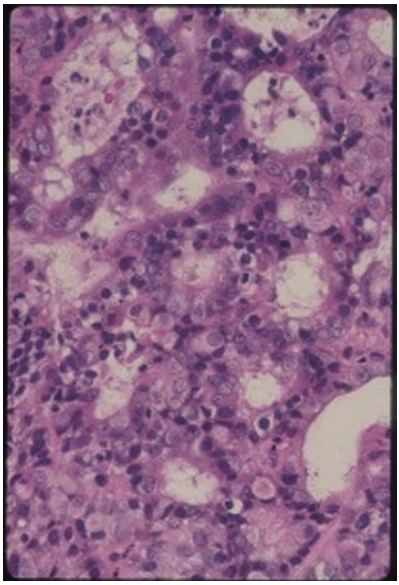

Fig. 9 Same endometrial biopsy: adenocarcinoma, endometrioid type with secretory features. H&E ×100

gestation. The histologic examination of the endometrial curettings revealed an endometrial adenocarcinoma in addition to the products of conception (chorionic villi) and endometrial stromal decidualization (Figs. 8 and 9). The malignant tumor probably developed in the hyperplastic endometrium associated with polycystic ovarian disease, most likely prior to the pregnancy. The association of malignant and gestational endometrial changes is very rare; it was suggested that it could be prevented by a previously inserted progestin intrauterine device [7].

2.3 Effects of Hormone Therapy on Benign Uterine Lesions

2.3.1 Leiomyomas

Leiomyomas are the most common benign tumors of the uterus, originating in the smooth muscle and in the vascular wall of the uterus. They form nodular masses located under the endometrium (submucosal), under the serosa (subserosal), in the myometrial wall (intramural), often reaching large dimensions. Once symptomatic due to sensations of heaviness, compression of neighboring organs such as urinary bladder or rectum, or protruding into the endometrial cavity causing abnormal vaginal bleeding by stretching the endometrium and increasing its surface, thus causing abundant menstrual shedding, surgery becomes the most indicated therapeutic choice.

Hormone therapy, however, is an alternative or a therapeutic adjuvant as uterine leiomyomas are strongly related to estrogenic influence, developing most commonly during the reproductive age and gradually shrinking after menopause. Gonadotropic-releasing hormone (GnRH) analogues have been used to reduce the size of leiomyomata by inducing an iatrogenic reversible menopause with up to 70% shrinking of their volume over a relatively short period of time. This therapy usually does not exceed 2–3 months as the size reduction generally takes place during this time, and side effects of an early menopause have to be minimized.

The mechanism of shrinking has been analyzed by histopathologic examination of the lesions in consecutive phases of treatment as compared to untreated (control) leiomyomas [8]. The central areas of the nodules display edema and hydropic degeneration that appears as "geographic" areas (Fig. 10) followed by collagen fiber

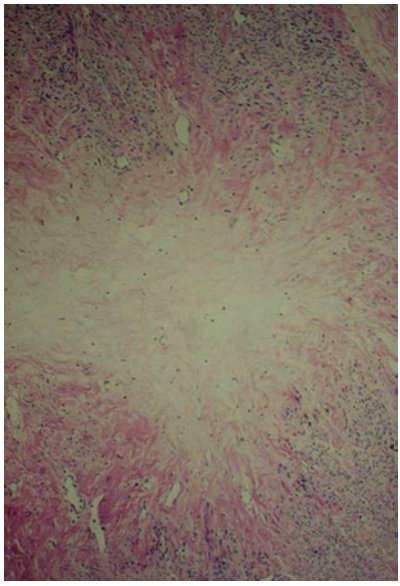

Fig. 10 Effect of 1-month Lupron therapy on leiomyoma: central edema, peripheral fibrosis. H&E ×25

proliferation and hyaline degeneration (Fig. 11). Necrosis of myometrial tissue surrounded by areas of hypercellularity was also present, with focal mild to moderate atypia. Lymphoid cell aggregates were observed in the treated cased and absent in the control. The interface between the myomatous nodule and the surrounding myometrium appeared blurred, with obliteration of the cleavage plan (Fig. 12a)—a change that may result in a more difficult surgical enucleation of the shrunken nodule. The edematous, hydropic, and necrotic areas become hyalinized forming confluent retracted scar-like plaques (Fig. 12b).

These histologic features when present in subsequent myomectomy or hysterectomy specimens are consistent with previous GnRH (Lupron) therapy resulting in smaller tumor masses at the time of surgery. The rather spectacular effect of size reduction with GnRH analogue therapy over a short period of time in most cases demonstrates the ability of the myometrial tissue to respond promptly to hormonal influences, due to hormone receptors present in the myometrial tissue. Therapy with GnRH analogues induces an iatrogenic menopause by suppressing the estrogenic stimulation as a result of decreased gonadotropin secretion. This response represents an accelerated version of the physiological postmenopausal shrinking over a longer period of time when both myomas and myometrium become smaller and eventually atrophic due to absent hormonal stimulation. Myomatous nodules in normally atrophic postmenopausal uteri are hyalinized and often calcified. Postmenopausal estrogenic stimulation may result in enlargement of myomatous uteri. Progesterone applied in intrauterine devices (IUD) or given as a contraceptive does not really reduce leiomyomas, but its effect on the endometrium is to stop proliferation and induce secretory changes, decidual reaction and eventually atrophy, and to stop the vaginal bleeding. On myomectomy and hysterectomy specimens,

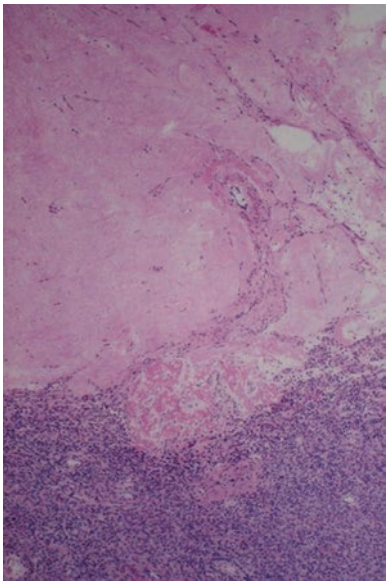

Fig. 11 Effect of 3-months Lupron therapy on leiomyoma: hyalinized retracted scar. H&E ×25

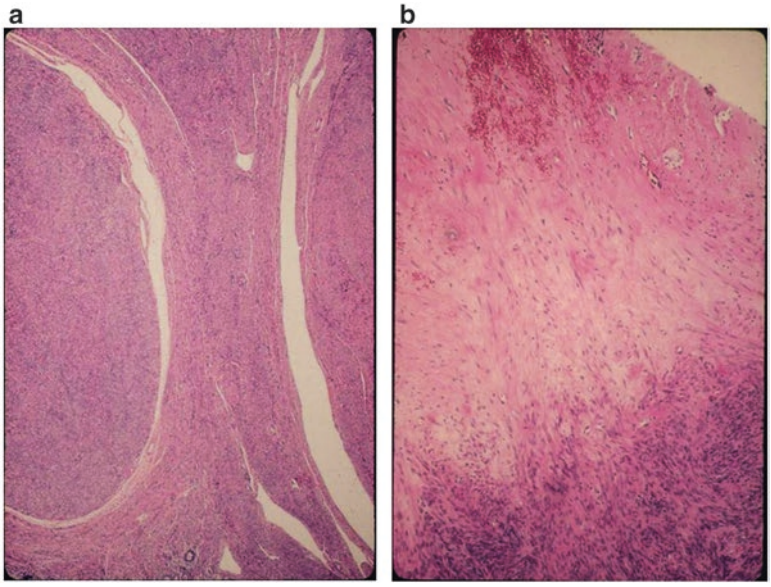

Fig. 12 (**a**) Untreated leiomyoma: cleavage plan at the myoma–myometrial interface. (**b**) Effect of Lupron therapy on leiomyoma: hyalinized zone of retraction obstructing cleavage plan from surrounding myometrium. H&E ×25

it has been shown that previous progesterone therapy elicited softening of the nodules, microscopically mild to moderate cellular atypia and occasional necrosis.

Ulipristol acetate aims also to shrink myomas in a way similar to GnRH, but its efficiency is not proven as yet [9].

Progesterone-receptor modulators (PRM) were evaluated in the management of endometriosis, adenomyosis, and leiomyomata due to their interaction with the progesterone receptor to inhibit or stimulate a downstream hormonal response. Their effect on endometrial histology included inactive or normal-appearing cyclic endometrium, discrepancy between glandular and stromal development, coexistent proliferative and secretory features, and occasional cystically dilated glands lined by a mixed mitotically active proliferative and a secretory endometrium; hyperplastic and neoplastic changes of the endometrium were not reported [4].

2.3.2 Adenomyosis

Adenomyosis is the presence of endometrial tissue (glands, stroma, and blood vessels) in the myometrium, which are also stimulated by estrogens and progesterone, therefore responsive to hormone therapy in a similar way as leiomyomas. With GnRH therapy and/or progesterone, there is shrinking of the affected regions in the uterus. Microscopically, the islands of endometrial tissue surrounded by myometrium

are gradually effaced with the glands becoming atrophic and the stroma dense and fibrotic, in a manner similar to the involution taking place after menopause.

2.3.3 Endometrial Polyps

These mostly benign endometrial lesions are a frequent cause of abnormal vaginal bleeding at any age but most commonly peri- and post-menopausal. Thickened blood vessels are central to a stalk surrounded by endometrial stroma and glands that are often cystic, both poor in hormone receptors, therefore maintaining the same structure throughout the menstrual cycle, occasionally causing intermenstrual vaginal bleeding. Hormonal contraceptive therapy does not elicit much change in the glands of the polyp which are keeping their mostly inactive appearance; their stroma is composed of fibroblasts and rich in collagen fibers. Postmenopausal polyps may be large due to cystic glandular dilation causing postmenopausal bleeding for which surgical removal is recommended. Hormone therapy is used in endometrial hyperplasia with polypoid growth (hyperplastic polyps) which is usually responsive to progesterone. The effects on the endometrium are evident as dose-dependent suppression of estrogen-induced mitotic activity and appearance of glandular secretion and stromal decidual reaction.

3 Hormone Replacement Therapy Effects on Uterus

With the prolongation of life expectancy, the postmenopausal period may last one-third or more of a woman's lifetime. Postmenopausal morbidity is chiefly caused by the gradual decrease followed by the absence of natural estrogen secretion due to regressing ovarian function. Among the most common symptoms are hot flashes, urogenital atrophy, insomnia, anxiety, osteoporosis, hyperlipidemia that may lead to threatening cardiovascular and cerebrovascular morbidity. Estrogens and estrogen derivatives were used for decades in the last century. In the 1970s, however it became clear that using estrogens alone or estrogen/progesterone sequentially, as an imitation of natural cyclic activity, during the reproductive years, is associated with a risk for endometrial hyperplasia and neoplasia [10, 11]. Since then, sequential hormone replacement therapy (HRT) was replaced with combined HRT for women who kept their uterus. This therapy has been administered on a large scale (to ~38% of women in the United States), despite multiple controversial opinions, and is permanently changing [12–14].

The estrogen/progesterone HRT regimens are different from those used for oral contraceptives, mainly because of the significantly lower dosages and the different hormonal types used. HRT is the object of numerous controversial opinions. The results of the largest randomized clinical trial of HRT by the Women Health Initiative (WHI) published in 2002 were surprising by showing an increase of postmenopausal morbidity (pulmonary emboli, coronary heart disease, stroke, breast cancer),

also suggesting deleterious effects from the associated progesterone [13]. This was contested by subsequent meta-analysis based on the evaluation of the patients age. It was concluded that HRT initiated early after menopause, in younger patients, and lasting not more than 5 years is rather beneficial, as older patients may have had cardiovascular disorders that are worsening, prior to the inception of HRT [14]. It was also proposed to lower the dosage of estrogen with presumably the same results. There are postmenopausal women who do not tolerate some side effects of progesterone and prefer the single estrogen replacement therapy (ERT) despite its known potential carcinogenic risks. The effect of HRT on the uterus depends on the type of hormone, its dosage, and duration. The currently applied HRT (transdermal estradiol and micronized progesterone), recommended by the guidelines from the North American Menopause Society [14], elicits a wide range of histopathological changes of the endometrial structure observed on biopsies or endometrial aspirates (Vabra), often difficult to interpret and to differentiate from premalignant and even malignant changes. The latter are not common in HRT but may occur with ERT. In HRT, sometime atypical hyperplastic and neoplastic changes are associated with masquerading features such as stromal decidual reaction of various extents, occasionally even imitating gestational changes.

3.1 Effects of ERT

Effects of ERT (estrogen alone, unopposed by progesterone) on the uterus are positively related to the duration of exposure. They are ranging from weakly to markedly proliferative endometrium, similar to the proliferative phase of the normally cycling endometrium. There may be associated breakdown of the stroma due to small thrombi in the blood vessels, manifested clinically by postmenopausal vaginal bleeding, histologically often designated rather vaguely as “irregular proliferative endometrium”. Prolonged use of this regimen may stimulate more proliferation of glands which appear crowded, lined by tall epithelial cells with large nuclei and displaying mitotic activity, as estrogens are mitogenic hormones. The crowded pattern is exaggerated by stromal breakdown.

The resulting pattern of “back to back” glands is suggestive of endometrial hyperplasia or neoplasia which has to be considered based on the presence of pseudo- and real epithelial stratification with loss of epithelial polarity, nuclear atypia, and atypical mitotic figures (Fig. 13a). Estrogen receptors are strongly positive (Fig. 13b). Crowding of otherwise benign fragmented glands or detached epithelial cells, due to the breakdown and disappearance of the intervening stroma, thrombosed blood vessels, and hemorrhagic areas are not uncommon. Other estrogenic effects on the endometrium is the formation of hyperplastic polyps growing on stalks with thick blood vessels, composed of hyperplastic glands that are more commonly not atypical and reversible. Squamoid metaplasia of endometrial glands, appearing as small nodules of polygonal eosinophilic epithelial cells, also called “morules” by analogy with (but not related to!) the early embryo, is also a prolonged

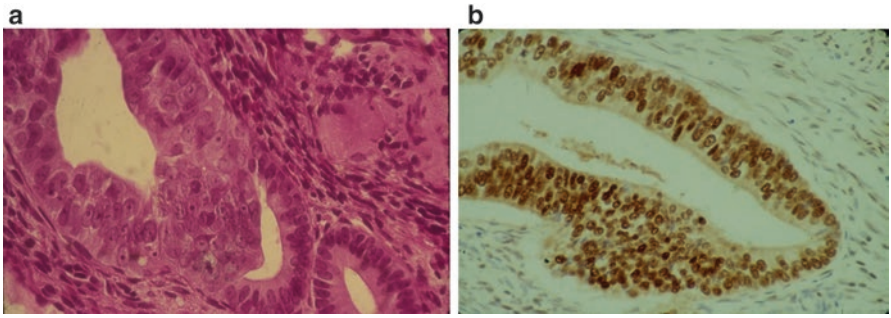

Fig. 13 (**a**) Effect of ERT on endometrium: atypical intraglandular hyperplasia with epithelial stratification, loss of polarity, nuclear atypia, mitotic activity. H&E ×100. (**b**) ERT effect on endometrium: Estrogen receptor stain strongly positive in atypical hyperplastic gland. Immunohistologic stain for ER ×100

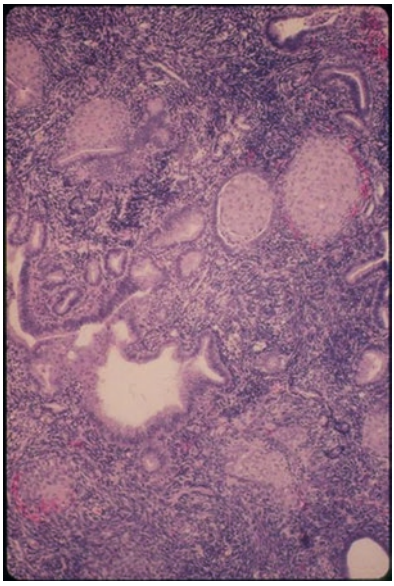

Fig. 14 ERT effect on endometrium: Atypical glandular hyperplasia with squamoid metaplasia (morules) H&E ×40

estrogen effect. These immature squamoid structures are usually metaplastic, therefore benign; they may fill the glands (Fig. 14) and appear as solid areas suggestive of, for the uninitiated, squamoid carcinoma especially when associated with atypical glandular hyperplasia. The endometrial stroma may respond to prolonged estrogen administration with accumulations of foamy macrophages with an abundant cytoplasm stuffed with lipid droplets representing deposits of steroid hormones. This finding in endometrial biopsies, although often associated with atypical hyperplasia or carcinoma, is in itself benign and may document a history of prior steroid hormone intake (Fig. 15).

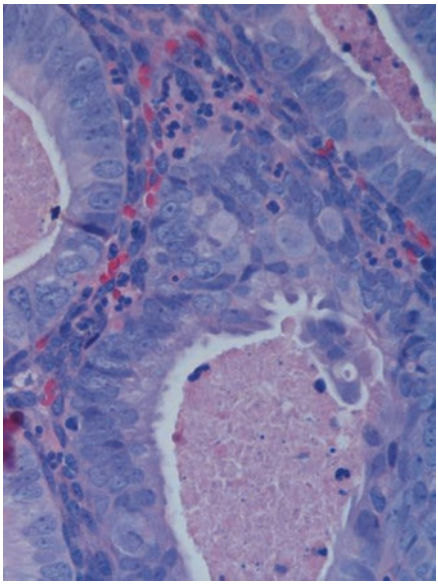

Fig. 15 ERT effect on endometrium: Atypical glandular hyperplasia and stromal foam cells H&E ×100

Prolonged ERT is also used in children with ambiguous genital development such as in Turner's syndrome at the time of puberty. The maternal hormones provide feminine development of Mullerian ducts during intrauterine life. At birth and in early childhood, the genital organs (uterus and fallopian tubes) are infantile and the absent ovaries are replaced by streak gonads. At the age of puberty, there is failure of menarche as the streak gonad failed to become an ovary due to the 45,XO karyotype lacking a second sex chromosome. No sex hormones are produced and the uterus remains infantile. Hormone replacement therapy is given to stimulate the uterine development and menarche at puberty.

As an example, a patient admitted to the emergency room with massive vaginal bleeding had been given ERT for 7 years (from the age of 12 to age 19). The uterus was found markedly enlarged containing polypous masses that histologically revealed an endometrioid adenocarcinoma for which hysterectomy was performed (Fig. 16a, b). Most, though not all, endometrial carcinomas developed during or after ERT are endometrioid (type I), strongly hormone receptor positive carcinomas with a rather favorable prognosis, as compared to the nonendometrioid (type II) seen less often in mostly older women, not treated with estrogens [15].

The effect of ERT after menopause on the myometrium is to stimulate, by receptor-binding to the myometrial tissue, the proliferation of myometrial tissue that may result in proliferating leiomyomas. Involution of the uterus and atrophy of the endometrium will take place after the cessation of hormone stimulation and/or exhaustion of hormone receptors.

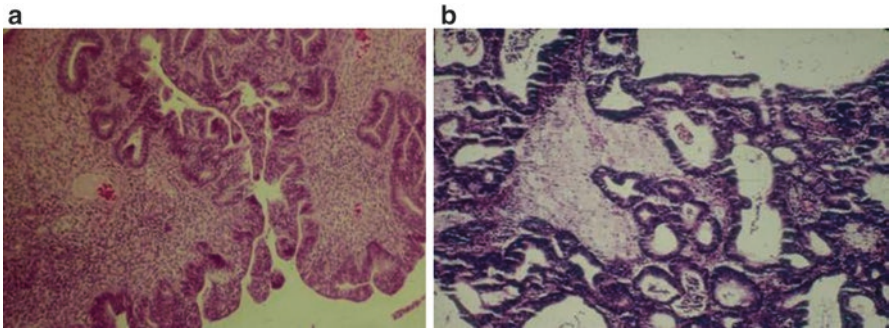

Fig. 16 (**a**) Effect of 7-year ERT duration on endometrial biopsy of a 19-year-old patient with Turner syndrome: well-differentiated adenocarcinoma, endometrioid type. H&E ×100. (**b**) Same patient, section of hysterectomy specimen: adenocarcinoma, endometrioid type H&E ×100

Table 2 Endometrial histology in HRT

Glands	Proliferative, weakly or as in early, mid or late proliferative phase
	Hyperplastic, without or with atypia, crowded, polypoid
	Secretory, early, mid or late
	Mixed proliferative and secretory
	Metaplasia: tubal (ciliated), squamoid (morules), mucinous, papillary
Stroma	Edematous
	Decidual reaction
	Breakdown as in menstrual shedding, hemorrhagic
Blood vessels	Spiral, thickened or thin
	Angiectasis, thrombosis
Any combination of the above	

3.2 Effects of Combined HRT

Effects of combined HRT on the uterus include a wide spectrum of structural changes (Table 2). Various combinations of proliferative and secretory patterns may be observed as a result of estrogenic and progesterone simultaneous stimulation: weakly to intensely proliferative glands and/or secretory glands with sub- and supranuclear secretory vacuoles and/or intraluminal secretion, consistent with various stages of glandular secretion. Associated secretory stromal changes range from edema to decidual reaction and compact decidualization analogous to gestational endometrium. The blood vessels range from thin and straight to thick and coiled similar to spiral arterioles seen in natural midsecretory endometrium. The overall histologic pattern may appear confusing when compared to the natural cyclic dating of the endometrium. Associated abnormal, though benign, histologic structures can include tubal (ciliated), eosinophilic, mucinous, or papillary metaplasia presenting an irregular pattern that especially when combined with glandular crowding may

appear suspicious for neoplasm (Fig. 17). Pseudomenstrual changes consisting of vascular fibrinoid thrombosis, stromal breakdown, apoptosis, cellular debris with "nuclear dust," stromal polymorphonuclear leukocytic infiltrates may occur at the iatrogenic withdrawal of hormones, in an analogous way to menstrual endometrial shedding. With the currently combined HRT recommended by the guidelines of the North American Menopause Society, transdermal estradiol and micronized progesterone [14] a commonly seen histological pattern is that of proliferative glands and secretory-type glands resulting from the simultaneous intake of estrogen and progesterone (Fig.18a, b). Coexisting proliferative glands with decidualized stroma reflect the obviously iatrogenic predominant effect of progesterone therapy, simultaneous with a moderate estrogen effect (Fig. 19a, b). Predominant estrogen effect may elicit benign tubal (ciliated) metaplasia (Fig. 20a) and tubal metaplasia associated with glandular atypia (Fig. 20b) as well as squamoid metaplasia, as previously shown (Fig. 14). Predominant progesterone effect may show a late secretory-type endometrium, with stromal breakdown somehow reminiscent of premenstrual changes (Fig. 21) or decidualized stroma with inactive epithelium, reminiscent of gestational epithelium (Fig. 22). Prolonged therapy with combined HRT in postmenopausal women may eventually result in inactive endometrium with straight nonproliferating and nonsecreting glands and dense stroma (Fig. 23). This finding can occasionally be associated with functional and/or hyperplastic changes.

It is presumed that neoplastic changes are prevented by adding progesterone to estrogen therapy. This is however not always the case. Endometrial cystic glandular hyperplasia and irregularly proliferative glands are a relatively common finding (Fig. 24). Atypical endometrial hyperplasia (Fig. 14) and endometrial carcinoma (Fig. 25) are occasionally seen in postmenopausal women receiving combined HRT

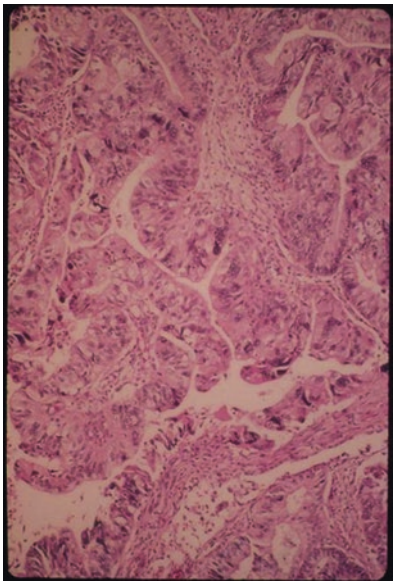

Fig. 17 Effect of combined HRT on endometrium: glandular crowding, mucinous, tubal, papillary metaplasia, nuclear atypia. H&E ×40

[16]. This can occur in some cases in which cyclic progesterone is administered for a shorter duration and in patients with risk factors such as obesity or estrogen-secreting ovarian tumors.

The effects of HRT on the endometrium are dose- and duration-dependent and reflect often in single samples puzzling features such as a combination of hormone depletion and hormone stimulation by both estrogens and progesterone.

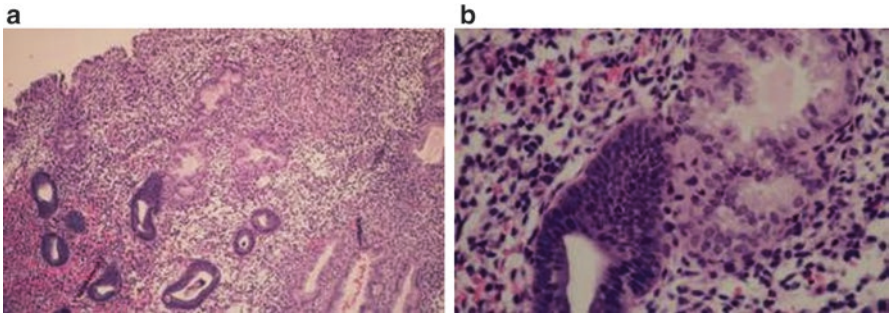

Fig. 18 Effect of combined HRT on endometrium: proliferative and secretory glands side by side. H&E ×40 (**a**) and 100 (**b**)

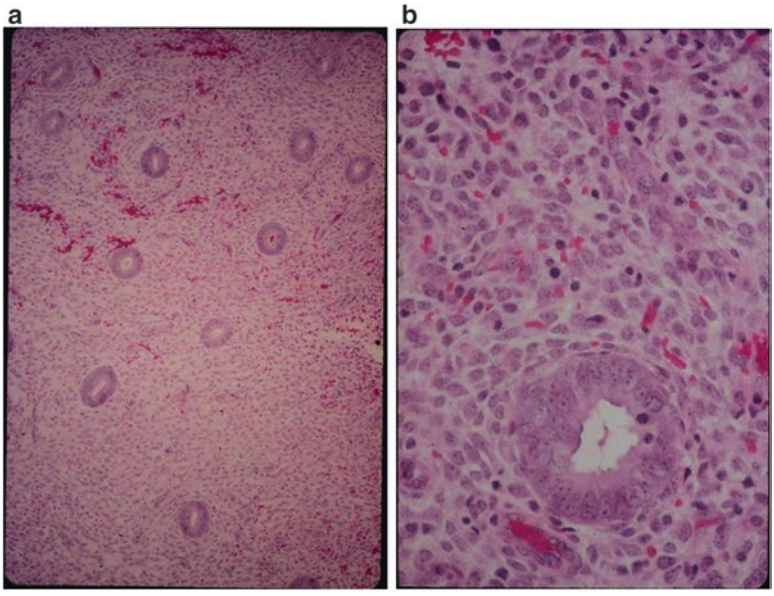

Fig. 19 (**a**) Effect of combined HRT on endometrium: stromal hyperplasia with decidual reaction and early proliferative-type glands. H&E ×25. (**b**) Effect of combined HRT on endometrium: proliferative gland with mitosis and decidualized stroma H&E ×100

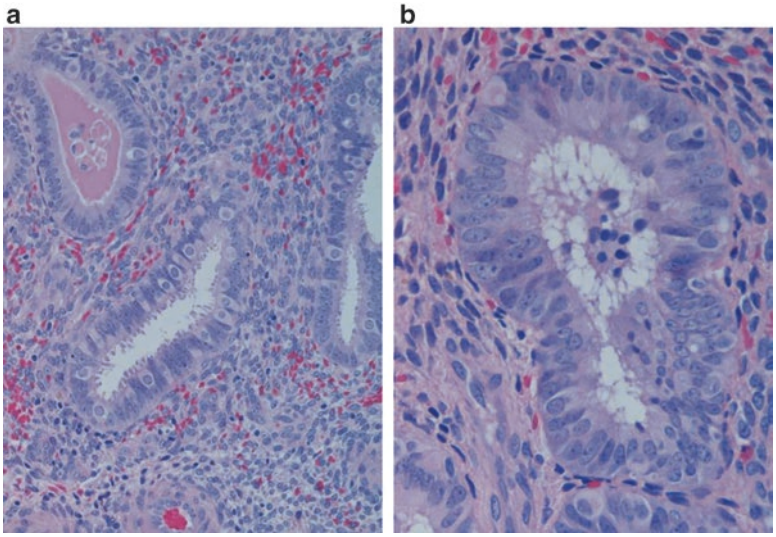

Fig. 20 (**a**) Combined HRT with predominant estrogen effect on endometrium: tubal metaplasia of glandular epithelium. H&E ×40. (**b**) Combined HRT with predominant estrogen effect on endometrium: Hyperplastic gland with tubal metaplasia and atypia. H&E ×100

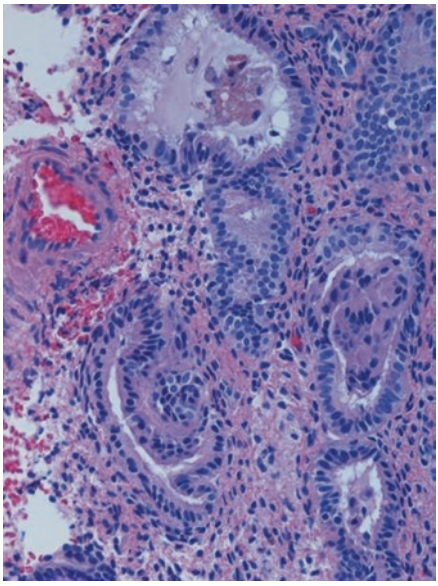

Fig. 21 Combined HRT with predominant progesterone effect on endometrium: secretory glands, early stromal breakdown. H&E ×40

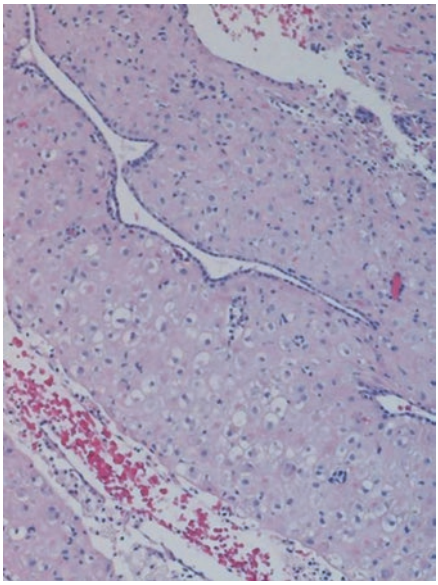

Fig. 22 Combined HRT with predominant progesterone effect on endometrium: decidualized stroma, inactive epithelium, similar to gestational endometrium. H&E ×25

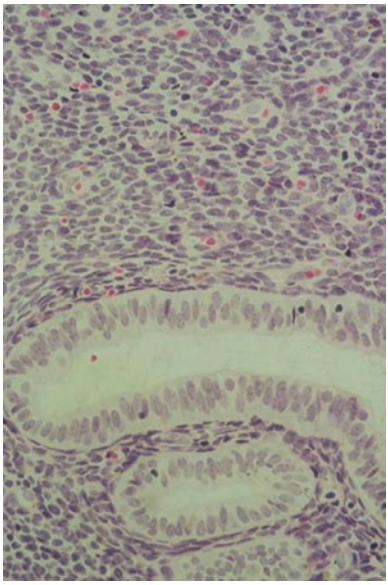

Fig. 23 Effect of prolonged HRT on endometrium: nonproliferative, nonsecretory inactive glands, dense stroma. H&E ×100

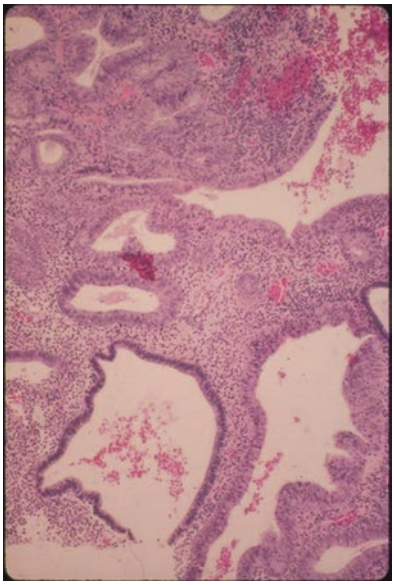

Fig. 24 Effect of combined HRT: Glandular cystic hyperplasia, focally atypical. H&E ×40

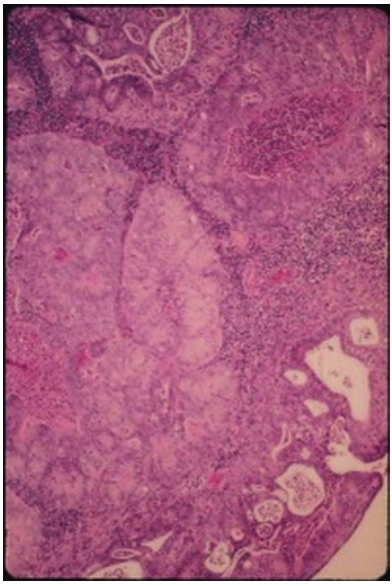

Fig. 25 Endometrial adenocarcinoma and glandular cystic hyperplasia in a 63-year-old patient receiving combined HRT for 7 years. H&E ×40

4 Effects of Antineoplastic Hormone Therapy

4.1 Progesterone Therapy

Progesterone therapy is often used in premenopausal patients diagnosed with endometrial hyperplasia based on its ability to inhibit DNA synthesis and to induce regression of abnormal endometrial proliferation. Medroxyprogesterone acetate (MPA) is the treatment of choice for endometrial glandular hyperplasia without atypia. High-dose progestins are also prescribed to reverse atypical glandular hyperplasia and as an adjuvant therapy for endometrial carcinoma especially for younger patients who want to preserve their uterus for reproductive purposes and for selected postmenopausal patients with contraindications for surgery [17].

The histologic response to progesterone therapy is mediated by progesterone receptors. The extent and intensity of the response correlates with the receptor level and distribution [18]. This therapy produces an arrest of glandular proliferation, epithelial secretory changes and stromal edema, and/or decidual reaction [19]. The endometrium appears quiescent with no or few mitoses in both glandular and stromal compartments. The blood vessels respond to progestins occasionally by thickening and coiling as in spiral arterioles. These changes however may be irregularly developed and alternate with areas of hyperplasia similar to those seen in the biopsies prior to therapy. Consecutive endometrial biopsies from patients diagnosed with endometrial hyperplasia treated with progesterone may show different histologic patterns with progressive decrease of hyperplasia especially in hyperplasia without atypia which is more responsive to this therapy.

The effect on the glandular epithelium is evident as secretory vacuoles, intraluminal secretion, stromal hyperplasia with decidual reaction and thickened arterioles, in various combinations. The volume of stromal tissue is increased compared to that of the glands. Cystic glands usually persist but may contain intraluminal secretion (Fig. 26a, b). The architectural changes due to prolonged and unopposed estrogenic stimulation in endometrial hyperplasia such as cystic dilation of the glands, irregular crowding, cribriforming, and outpouching tend to persist after progesterone therapy, while the epithelial lining of the glands appears more responsive: mitotic activity is decreased or absent, nuclei are regular and cells appear quiescent. In atypical endometrial glandular hyperplasia and in endometrial carcinoma adjuvant, progesterone therapy may fail to produce any effect or may produce only partial or focal change.

A 32-year-old patient with endometrial carcinoma refused surgical therapy and received high-dose progesterone (Megace) for 3 months. The endometrial biopsy showed partial secretory changes of the glands in this endometrioid adenocarcinoma (Fig. 27a). After subsequent 3 months of Megace therapy, the cribriform pattern persisted while the glands were secretory appearing quiescent, with no mitotic activity (Fig. 27b). Six months later, on the same therapy, the cribriform pattern persisted while the secretory changes became diffuse (Fig. 28). Hysterectomy was performed and histologic sections of the uterine wall displayed myometrial invasion

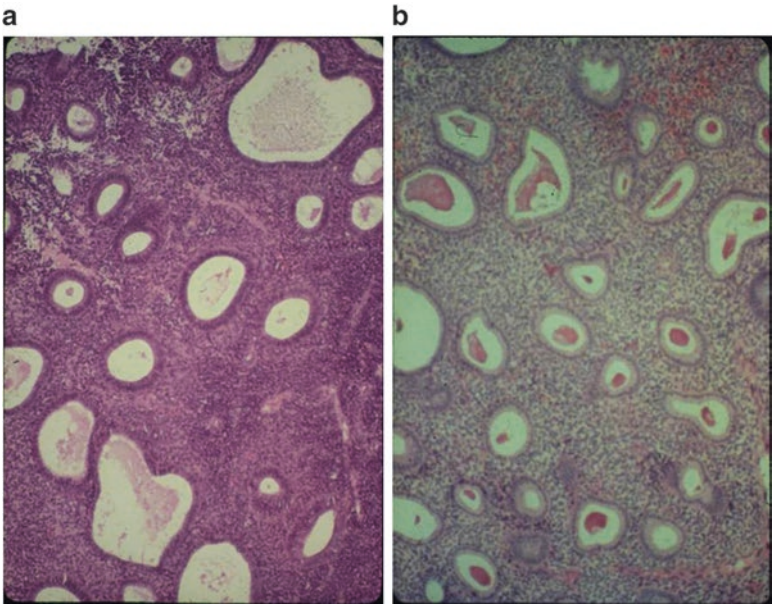

Fig. 26 (**a**) Nonatypical endometrial glandular-cystic hyperplasia, before HRT: proliferative epithelial lining of cysts. H&E ×40. (**b**) Same patient after 3 months of progesterone therapy: glandular cysts persist, lined by secretory epithelium, intraluminal secretion

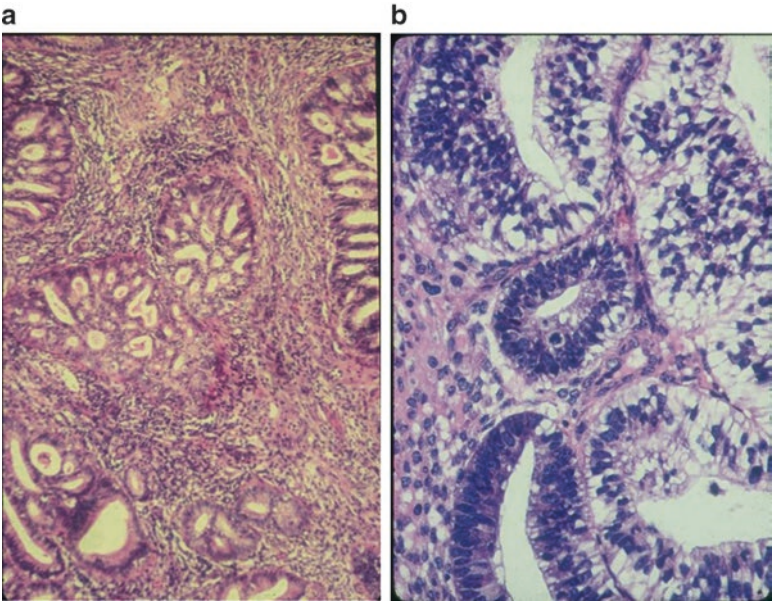

Fig. 27 (**a**) Endometrial biopsy of a 32-year-old patient: adenocarcinoma, endometrioid type. H&E ×25. (**b**) Same patient, endometrial biopsy after 3 months Megace therapy: secretory changes in neoplastic glands H&E ×100

by endometrioid adenocarcinoma with secretory glands ("secretory carcinoma" as it is called in some classifications) involving almost the full thickness of the uterine wall (Fig. 29).

In another 28-year-old obese patient diagnosed with endometrial adenocarcinoma, endometrioid type, the endometrial biopsy after 3 months of progesterone therapy showed on some histologic sections decidual tissue (Fig. 30), while on other sections cribriform glands with secretory changes were surrounded by a decidualized stroma (Fig. 31). On hysterectomy however, no invasive tumor was identified.

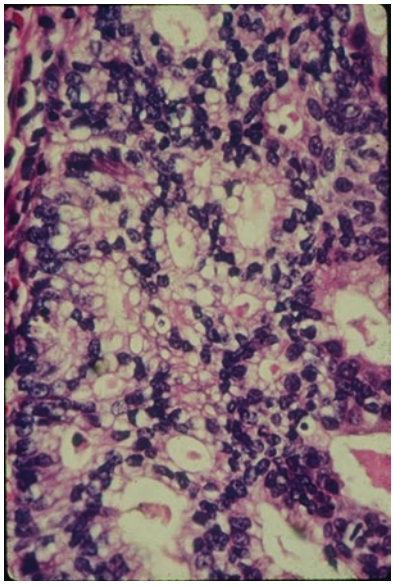

Fig. 28 Same patient after 6 months more of Megace therapy: endometrial adenocarcinoma with secretory changes. H&E ×100

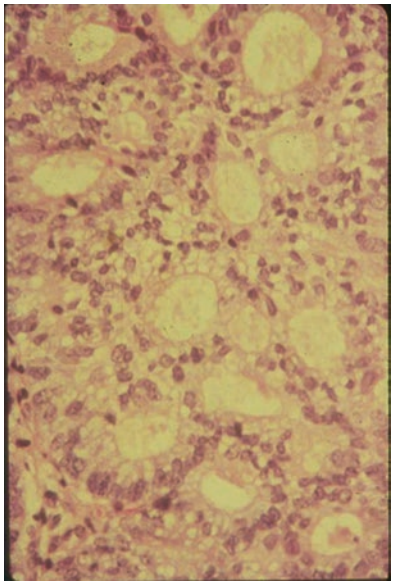

Fig. 29 Same patient after 2 months more of Megace therapy, section of hysterectomy specimen with diffuse myometrial invasion by adenocarcinoma displaying extensive secretory changes (secretory adenocarcinoma). H&E ×100

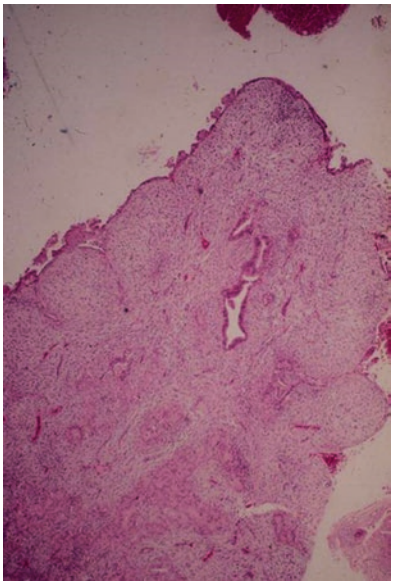

Fig. 30 Endometrial biopsy of a 28-year-old obese patient diagnosed with endometrial carcinoma, after 3 months Megace therapy: areas of diffuse stromal decidualizaton, some inactive glands. H&E ×25

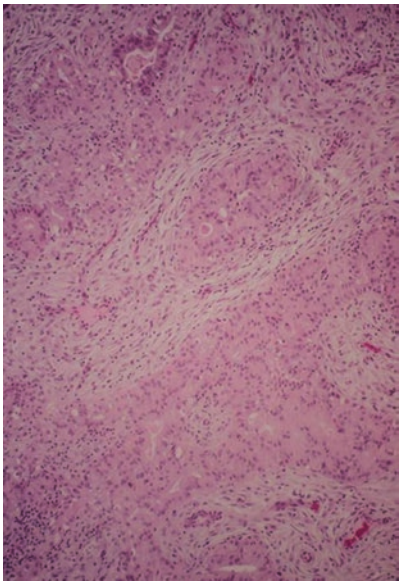

Fig. 31 Same biopsy (as in Fig. 30): adenocarcinoma, endometrioid type with secretory changes (secretory carcinoma) and stromal decidualization. H&E ×25

A "pseudopregnancy" histologic pattern (decidua, secretory glands) on endometrial biopsies therefore may be misleading by masquerading malignant changes.

Only careful and detailed examination of the hysterectomy specimen can rule out malignancy. Complete reversal of endometrial carcinoma by hormonal therapy is

still a subject of debate, as is preservation of fertility in young women with endometrial neoplasia [20–23].

4.2 Tamoxifen Therapy for Breast Cancer

Tamoxifen is a nonsteroidal, synthetic triethylene estrogen derivative used successfully in the adjuvant therapy and prophylaxis of breast cancer. It binds to estrogen receptors in a manner similar to that of estradiol and induces binding of the tamoxifen/receptor complex to the nuclear DNA, resulting in a decrease of available unbound receptors. This explains the antiestrogenic effect on breast tissue. Its effect on the uterus is more complicated, being both antagonistic and agonistic to that of estrogens. The estrogen-agonist effect on the uterus is manifested by polypous proliferation with or without endometrial glandular hyperplasia ranging from cystic and nonatypical to atypical glands; areas of frank neoplasm in the polyps are occasionally present [24]. The stroma is different from that of endometrial hyperplastic polyps associated with a hyperestrogenic clinical background which display vascular and fibroblastic proliferation. Tamoxifen-related endometrial polyps usually display a mostly fibrotic stroma with few fibroblasts and often mucinous metaplasia of glands (Fig. 32a) as compared to nontreated endometrial polyps (Fig. 32b).

In the largest published histologic study of 700 cases of endometrial tissue from biopsies and hysterectomy specimens taken from patients treated with tamoxifen

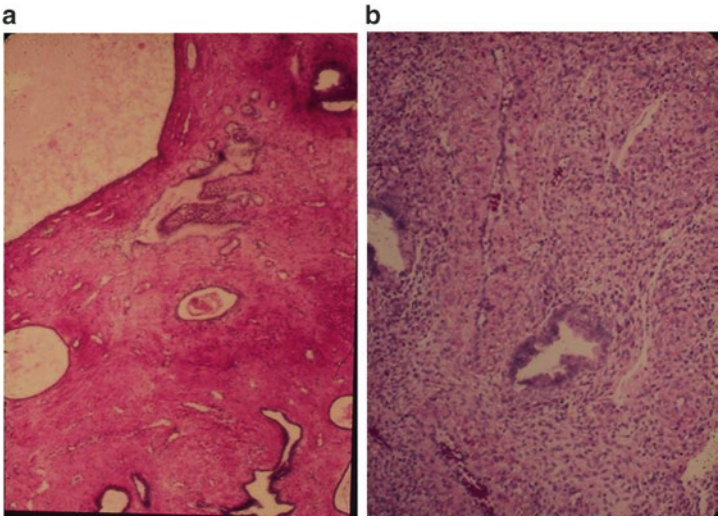

Fig. 32 (**a**) Patient treated with tamoxifen for breast cancer: endometrial polyp with cystic glands, mucinous metaplasia, and fibrous stroma. H&E ×25. (**b**) Endometrial polyp, no previous tamoxifen therapy: vascular thickening, endometrial inactive glands, and cellular stroma. H&E ×40

for breast cancer [25], the majority (64%) showed normal cycling or inactive endometrium. A significant number of patients (about 24%) had endometrial polyps composed of mostly inactive glands, some with mucinous metaplasia and some with benign hyperplastic changes, often cystically dilated (Fig. 31). Malignant changes were diagnosed in 4.7% of all cases, most often high-grade serous endometrial adenocarcinoma, interestingly enough not associated with atypical glandular hyperplasia as is the case in most estrogen-dependent endometrial carcinomas. Endometrial carcinoma was present in polyps displaying benign cystic changes and a fibrotic stroma (Fig. 33), with no background of glandular hyperplasia.

This is a different pattern from that of endometrial polyps involved by endometrioid carcinoma, usually associated with atypical hyperplasia. Only a third of the malignant endometrial cancers were endometrioid carcinomas (which overall are the majority of endometrial neoplasms), while two-thirds were poorly differentiated serous carcinomas (Fig. 34a, b). It seems therefore that both benign polyps and malignant endometrial neoplasms are histologically and biologically different from what is generally accepted as an estrogen-related endometrial neoplastic growth. This may be due possibly to different receptors: alpha-estradiol receptors in hyperestrogenic patients and beta-estradiol receptors in tamoxifen-treated patients. Also the proliferation of subendometrial nonglandular tissue which often mimics an endometrial thickening on ultrasound uterine images [26], raising suspicion of endometrial hyperplasia, is unrelated to Estradiol (E2 alpha) receptors. Multiple endometrial cancer reported cases associated with tamoxifen therapy were high grade neoplasms, including malignant mixed Muellerian tumors [27–29]. Increased

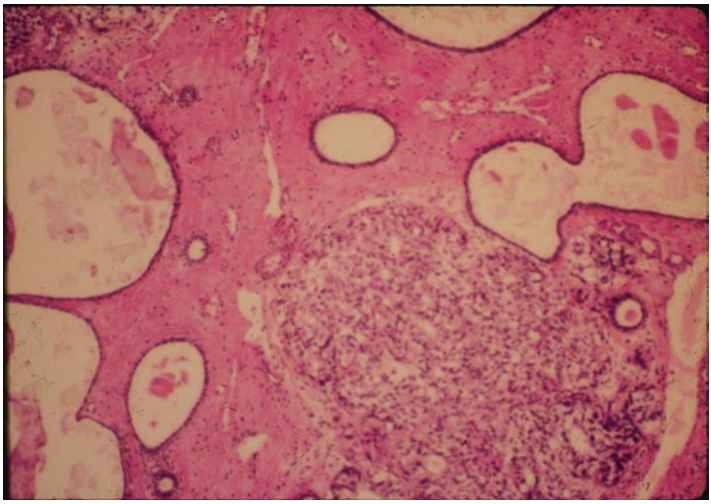

Fig. 33 Patient treated with tamoxifen for breast cancer: endometrial polyp with area of poorly differentiated adenocarcinoma and benign cystic glands in fibrotic stroma. H&E ×25

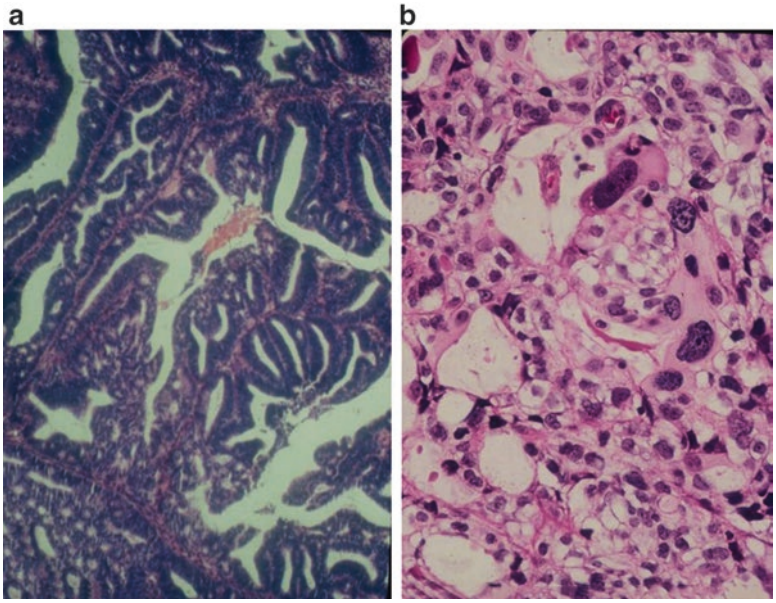

Fig. 34 (**a**) Patient treated with tamoxifen for breast cancer. Endometrial biopsy: adenocarcinoma, endometrioid type H&E ×40. (**b**) Patient treated with tamoxifen for breast cancer. Endometrial biopsy: high-grade serous carcinoma H&E ×100

aggressiveness of endometrial cancer has been associated with tamoxifen therapy due to recently identified genetic changes [30]. Tamoxifen-treated patients diagnosed with endometrial cancer were more common in older patients and in those who had a longer duration of therapy [25].

The estrogen-agonist effect of tamoxifen on the myometrium may include diffuse smooth muscle hyperplasia of the uterus (myohyperplasia), leiomyomata, adenomyosis with or without glandular hyperplasia. The size of the uterus may increase considerably in some cases reaching over 1200 g (Fig. 35a, b).

Despite the undesirable side effects of tamoxifen therapy on the uterus, it is now considered that the benefits (prevention of contralateral breast cancer recurrence, beneficial effect on cardiovascular and skeletal systems) exceed its deleterious side effects. It has been suggested that adding intrauterine levonogestrel to the tamoxifen therapy of breast cancer may prevent the risk of endometrial neoplasm [31]. Early detection of uterine malignancy is possible with careful surveillance including hysteroscopy, ultrasound examinations, and endometrial biopsies [32, 33] (Table 3).

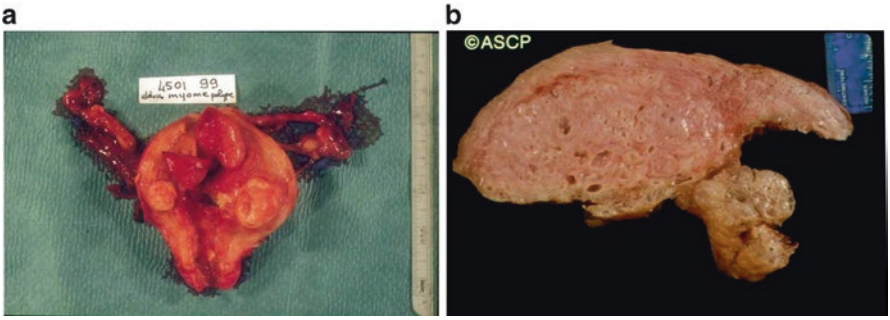

Fig. 35 (**a**) Patient treated with tamoxifen for breast cancer: massively enlarged uterus (980 g) with multiple leiomyomas and adenomyosis. (**b**) Patient treated with tamoxifen for breast cancer: massively enlarged uterus (1220 g) with diffuse adenomyosis and large endometrial polyp

Table 3 Tamoxifen therapy for breast cancer: effects on uterus

Endometrial cyclic changes
Inactive/atrophic endometrium
Metaplasia (mucinous most often)
Estrogen-agonist effects: leiomyoma, adenomyosis, myohyperplasia
Endometrial polyps with cystic and mostly non-atypical hyperplasia
Malignant tumors: endometrioid, serous high-grade carcinoma, malignant mixed Muellerian tumors (MMMT)

5 Conclusions

The diagnosis of uterine tissue, mostly of endometrial biopsies, from patients undergoing hormone therapy is often confusing and difficult to interpret [34]. This chapter presents a contemporary analysis meant to clarify the most commonly encountered issues, including oral contraception, ovarian stimulation, hormone replacement therapy, and antitumoral hormone therapy.

The histopathological patterns observed in the frequently taken endometrial biopsies from patients on hormone therapy encompass a wide variety of changes that cannot be sufficiently and adequately described in textbooks. They do not fit the classical descriptions of pathological noniatrogenic entities because of their diversity and the permanent change of therapeutic regimens, dosages as well as new concepts of therapy which represent challenges for both users and medical prescribers. A close clinical–pathological correlation and experience in gynecologic pathology is necessary for the interpretation of the often puzzling microscopic features of endometrial biopsies from hormonally treated patients.

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