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Review

A review of the endometrial histologic effects of progestins and progesterone receptor modulators in reproductive age women

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Abstract

This review compares the histologic changes that occur in the endometrium following ovulation and progesterone secretion with contraceptive progestins and progesterone receptor modulators (PRMs) that may be used as contraceptive agents in women. The morphologic endometrial changes vary by the progestin type, dosage and duration; are often subtle and difficult to interpret; and may also vary depending on whether or not estrogen is used.

The prolonged use of ethinyl estradiol and a progestin as a combined oral contraceptive results in common endometrial histologic findings that include glandular and stromal atrophy and spiral arteriole underdevelopment. Intrauterine systems releasing levonorgestrel have similar changes that are related to the proximity of the device to the endometrium, while progestin-only implants result in atrophy with marked vascular changes characterized by underdevelopment of spiral arterioles and dilated, thin-walled vessels near the surface epithelium. Lower doses of levonorgestrel delivered by a vaginal ring allow ovulation, and the endometrial changes appear to reflect the impact of the endogenous hormones.

PRMs have been investigated as potential female contraceptives. PRM-associated endometrial changes include an inactive endometrium with cystically dilated glands, lined by epithelium with increased apoptosis in a background of compact nondecidualized stroma. Histologic differences between PRMs appear to depend on the degree of progesterone receptor agonistic activity.

Keywords: Progesterone; Progestins; Selective progesterone receptor modulators; Endometrium; Histology; Contraceptive

1. Introduction

Exogenous steroids with estrogenic, androgenic and progestogenic activity are commonly used as female contraceptives. These steroids induce a spectrum of histologic changes in endometrial glandular and stromal architecture, blood vessels and cytology that differ from those that occur during the normal menstrual cycle. The morphologic changes vary by hormone type, dosage and duration; are often subtle and difficult to interpret; and may also vary depending on whether or not estrogen is used. The progesterone receptor modulators (PRMs) mifepristone and ulipristal acetate (UPA) have the potential to be used as female contraceptives but they result in unique endometrial histology known as PRM-associated endometrial changes (PAECs). The endometrial morphologic changes may be reflected in unscheduled bleeding, contraceptive efficacy or both. The purpose of this review is to describe the varying endometrial histologic changes of progestins used as hormonal contraceptive, used with or without estrogen and PRMs.

2. Normal menstrual cycle endometrial changes

Endometrial tissues undergo continual changes resulting from endogenous ovarian hormonal secretion and the interaction of these hormones with their respective receptors [1]. The endometrial histology is further modified by the ratio of estradiol to progesterone, their receptor concentrations [2] and the location within the uterus, since the lower uterine

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segment is less responsive to hormonal stimulation compared to the fundus [3,4].

The endometrial functional layer (stratum functionalis) is the upper two thirds [5] that undergoes characteristic changes of proliferation, secretion and degeneration during the ovarian cycle [5,6]. The basal layer is retained during menstruation and is the source of stem cells, epithelial cells and stromal cells that regenerate the functional layer [7]. The demarcation between functional and basal layers is well described both in primates [8] and humans with the onset of menstruation [9,10], but there is no clear-cut morphologic separation between the two layers.

The epithelium (glandular and luminal) and mesenchyme (stroma and vasculature) undergo specific morphologic changes, with proliferation in response to estradiol, and secretory differentiation attributed to progesterone [11] (Figs. 1 and 2).

The withdrawal of estradiol and progesterone results in endometrial breakdown with bleeding, cellular dissolution and shedding (menstruation) [12]. Recent studies implicate local inflammation in initiating endometrial breakdown and menstruation. Progesterone withdrawal initiates an influx of leukocytes, which result in local release of proteases, chemokines and cytokines [13,14]. The increased synthesis of endometrial matrix metalloproteinases leads to breakdown of the interstitial collagen, with associated loss of vascular support resulting in local thrombosis and loss of endometrial integrity followed by endometrial shedding [15].

The cessation of menstruation is thought to be due to re-epithelization of the luminal epithelium, which is brought about by a rapid proliferation of the glandular and luminal epithelial cells initiated through local growth factors and later by endogenous estradiol [16]. The glands and vessels become sinuous in the proliferative phase as their growth "outstrips" that of the stroma [17].

The estrogen-primed endometrium responds to postovulatory progesterone secretion with histologic findings that can be divided into interval, early, mid and late secretory phases [2] (Fig. 2). Epithelial cells retain proliferative nuclear features while demonstrating nonuniform subnuclear vacuolization during the interval phase on postovulatory day (POD) 0-2 [18]. The early secretory phase (POD 2-5) is characterized by the presence of subnuclear vacuoles in at least 50% of glandular epithelial cells, with progression of vacuoles to a supranuclear position followed by secretion into the gland lumen [19]. The pseudostratified appearance of the proliferative-phase glandular epithelial cells is lost as the nuclei move apart to form a single layer [20]. Arterioles begin to develop a spiral configuration as their growth outstrips the thickness of the functional layer [21]. The mid-secretory phase (POD 5-9) is characterized by coiled glands with luminal secretions, lined by nonvacuolated epithelium with round and vesicular nuclei, in a background of spindled edematous stroma [22]. The late secretory phase (POD 10-14) is characterized by stromal predecidualization and stromal infiltration by "granulocytes," now known to be uterine natural killer cells of lymphoid origin [23]. The spiral arteries become prominent, and large clear cells initially surrounding blood vessels appear in the stroma identified as early or predecidual changes. These cellular changes, reflecting continued progesterone secretion, extend outward and eventually become confluent [24]. Stromal breakdown and thrombi within disrupted endometrial vessels, followed by shedding of the functional layer, occurs with the withdrawal of estradiol and progesterone as the corpus luteum wans [6,9,10].

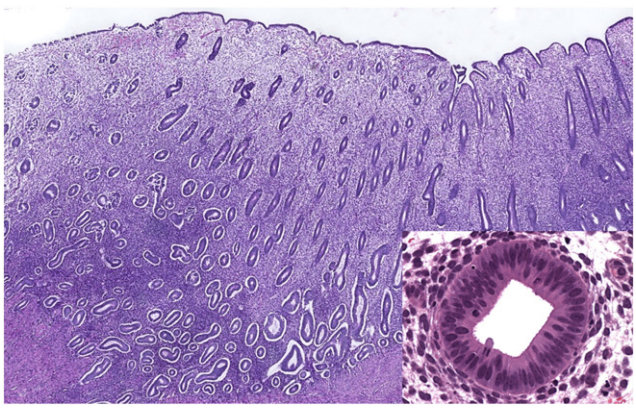

Fig. 1. Proliferative phase: glands are of simple tubular morphology and are evenly distributed in loose stroma. Mitotic activity is widespread in glands (see the inset) and stroma. Inset: proliferative-phase gland.

3. Endometrial effects of combination estrogen/progestin contraceptives

Combination oral contraceptives demonstrate the effects of both exogenous estrogen and progestin, with a dominant progestin-only effect "pill endometrium" depending on the length of use of the combined oral contraceptive (COC). Progestins in the first few cycles of use induce secretory differentiation, with coexistent proliferative and secretory features. The progestin down-regulates the estrogen receptor after several cycles and a "classic pill endometrium" occurs, composed of quiescent, atrophic glandular epithelium against a background of tortuous glands similar to secretory phase. The use of progestin-only methods such as injections or implants early on induces stromal cells with plump pink cytoplasm and distinct cell borders, known as decidualization, that are similar to changes seen in early pregnancy [22] (Fig. 3), but atrophy of both glands and stroma occur with continued use.

The 19-nor steroids with progestational biologic activity used in COC initially result in hyperinvoluted glands in an inert stroma. There are no consistent histologic features that allow differentiation between the endometrial and vascular effects of the various 19-nor steroids [25]. The 17-alpha-acetoxyprogesterone derivatives, when used alone, tend to produce similar but less prominent progestational effects than those of the combined 19-nor steroids with ethinyl estradiol estrogen.

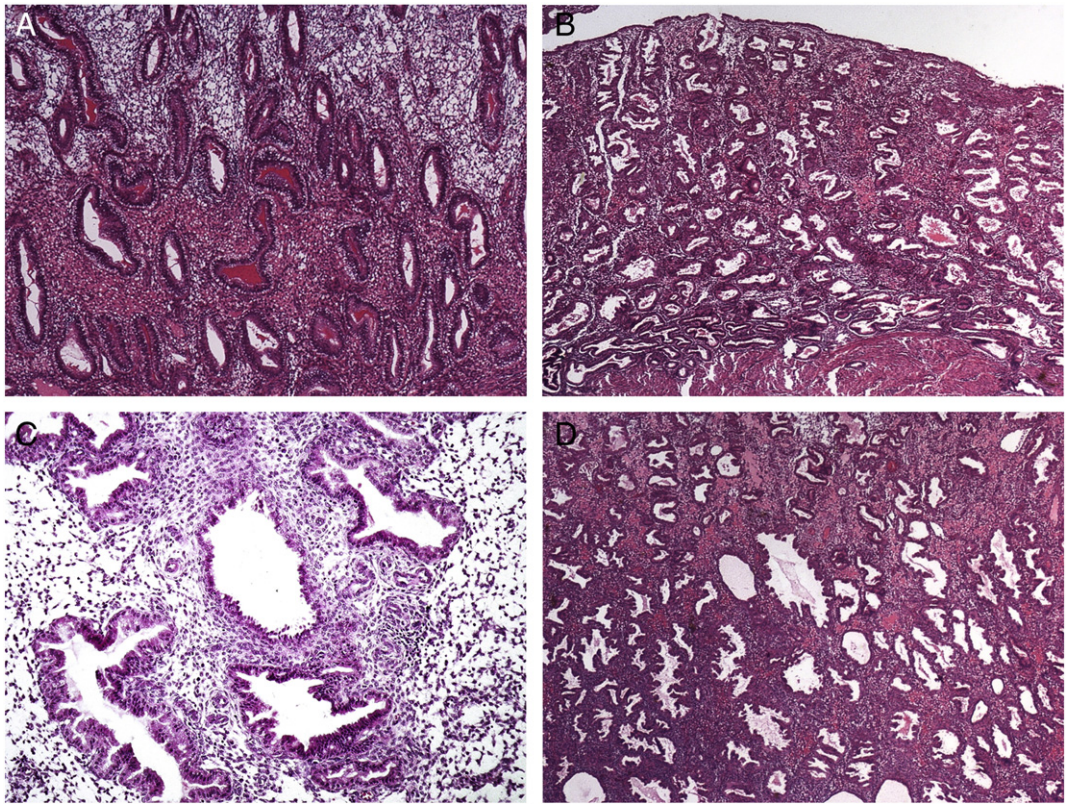

Fig. 2. (A) Early secretory phase — glands are of simple morphology, some having a serpentine course and there is subnuclear vacuolation. Stroma is loose and nondecidualized, with spiral vessels beginning to develop. (B) Mid-secretory phase — glands in the functionalis have a serpentine or tortuous profile and show active secretion. In contrast, the basal glands are of simpler morphology and show no secretory differentiation. (C) Mid-secretory phase vessels — predecidual stromal change can be seen extending outward from spiral arterioles. Glands show a complex folded appearance with active secretion. (D) Late secretory phase — glands are complex and tortuous ("accordion pleated") and set within stroma showing decidual change. Secretory product is present in gland lumina, some showing mild dilatation.

A combined injectable monthly method using estradiol cypionate 5.0 mg plus medroxyprogesterone acetate 25 mg (Cyclofem) was compared to depomedroxyprogesterone acetate (DMPA) 150 mg, a three monthly injectable. Atrophic endometrium was demonstrated after 3–6 months in 57% vs. 34% of the DMPA and Cyclofem users, respectively. There was a significant decrease in the density of the endometrial blood vessels in both DMPA and Cyclofem users, which consisted of dilated, thin-walled superficial microvessels but were associated with less unscheduled endometrial bleeding than in progestin-only users [26].

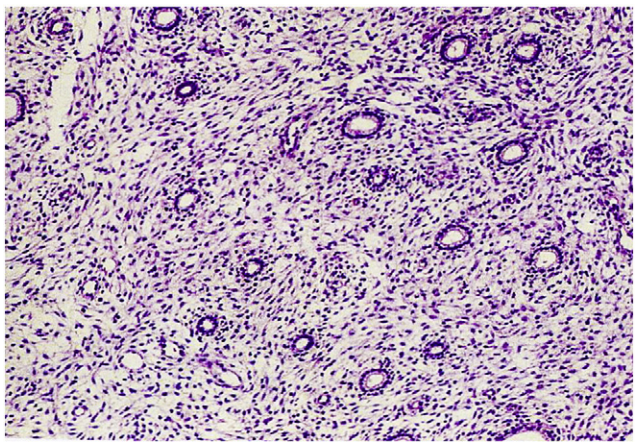

Fig. 3. COC pill effect. Endometrial glands show a simple tubular structure, the epithelial cells having inactive appearances with absence of mitotic figures and nuclear stratification. Weak secretory vacuolation is present in the cytoplasm. Glands are widely spaced in sparsely cellular endometrial stroma showing early pseudodecidualization.

4. Endometrial effects with progestin-only contraceptives

The primary mechanism of fertility regulation with progestin-only contraception consists of increased cervical mucus viscosity, as ovulation may not be consistently inhibited [27]. Endometrial changes that occur with progestin-only therapy are highly variable and depend on dose, type of progestin, duration of therapy, the degree of inhibition of follicular activity and whether or not ovulation occurs. The vascular changes are significant in that progestin-only implants have more superficial blood vessel fragility resulting in unscheduled breakthrough bleeding [25].

4.1. Oral progestin-only pills

Progestin-only pills are used daily orally without a pill-free interval [27]. Endometrial histology may demonstrate a proliferative pattern when estradiol is secreted by the developing

follicle and/or corpus luteum progesterone is decreased or absent. The secretory pattern, when present, superficially resembles the secretory phase of the normal menstrual cycle, but glandular and stromal development lag compared to that expected on a given day of a normal cycle. Glands appear underdeveloped and the stroma lacks the intermediate edematous changes found in a normal secretory phase. An atrophic pattern is common after prolonged use of progestin-only contraceptives, and it consists of small and scant glands that lose their tortuosity and are lined by low columnar epithelium in a background of enlarged ovoid stromal cells with indistinct borders. The vessels of the superficial endometrium are thin-walled and ectatic. The glands are small and indistinct in more abundant stroma compared to physiologic endometrial atrophy [28]. Norethindrone (NET) 300 mcg/day for a total of 3 months resulted in a variety of endometrial histologic changes occurring irrespective of ovarian function, including proliferative activity, suppressed proliferation, irregular secretion and atrophy [29]. A study of desogestrel 75 mcg/day for a total of 6 weeks showed a spectrum of endometrial changes in biopsies: proliferative endometrium, decidual transformation and glandular atrophy [30]. The differences in these two studies reflect the fact that desogestrel highly suppresses ovulation while NET at this dose has been found to inhibit ovulation only 35% of the time.

4.2. Subcutaneous implants: etonogestrel or levonorgestrel

Levonorgestrel tends to induce a wider spectrum of endometrial effects than etonogestrel. A study in users of levonorgestrel subcutaneous implants demonstrated histology ranging from atrophic changes, evidence of endometrial shedding, effects of progestins to proliferation. A few tissue samples demonstrated early, mid or late secretory changes [31]. There is a lack of specific histologic effect between the progestins due to subjective interpretation of the endometrium and a lack of quantitative assessment of the endometrium [32]. Both etonogestrel and levonorgestrel have similar endometrial histologic findings after 12 months of use [33]. Levonorgestrel implants result in an increased density of dilated, thin-walled fragile blood vessels that lead to the early onset of unscheduled bleeding [25].

4.3. Injectable DMPA

DMPA, an injectable contraceptive, is administered intramuscularly every 3 months, and it induces endometrial changes that initially have an exaggerated gestational-type glandular hyperplasia with marked nuclear changes, in a background of decidualized stroma. The stroma displays progestational effects after the first 6 months of use, but further treatment results in endometrial atrophy [34].

As mentioned above, DMPA was shown to result in the decrease of the density of the endometrial blood vessels, which consisted of dilated, thin-walled superficial microvessels [26]. Women using DMPA were found to have increased number of leukocytes in the endometrium associated with unscheduled bleeding compared to those with amenorrhea, suggesting a role for inflammation in the unscheduled bleeding [23,35].

4.4. Intrauterine systems releasing levonorgestrel

The levonorgestrel-releasing intrauterine system (LNG-IUS) produces atrophy of the glandular epithelium, prominent decidualization of the stroma and suppression of spiral artery formation as well as large, thin-walled, dilated vessels (Fig. 4) [29]. Women using the LNG-IUS had endometrial tissue obtained between 3 months and 7 years after insertion. The endometrial histology demonstrated glandular atrophy and decidualized stroma in all samples with evidence of inflammation and necrosis. Endometrial morphology returned to normal 1–3 months after removal of the LNG-IUS [36]. The most common histologic features with use of the LNG-IUS are stromal decidualization (96%), glandular atrophy (87%) and stromal inflammatory cell infiltration (79%), with other stromal findings including myxoid change and hemosiderin pigment [37]. The histologic findings vary according to the distance from and contact with the IUS, reflecting a concentration gradient of levonorgestrel within the tissue. The endometrium closest to the IUS had cushions of edematous, spindle-celled pseudodecidualization, and occasionally surface micropapillae, while the endometrium remote from the device displayed a less intensely decidualized stroma with spindle cells. Endometrium closest to the device showed glands with a cuboidal-to-columnar epithelial lining in a background of stromal decidualization characterized by rounder cells as opposed to spindled. A few of the specimens were interpreted as having hemorrhagic infarction, necrobiosis or coagulative necrosis [38].

4.5. Intravaginal rings

An intravaginal ring (IVR) releasing levonorgestrel 20 mcg/day was studied for the effect on the endometrium after 90 days of exposure. Endometrial tissues were obtained at days 23–25,

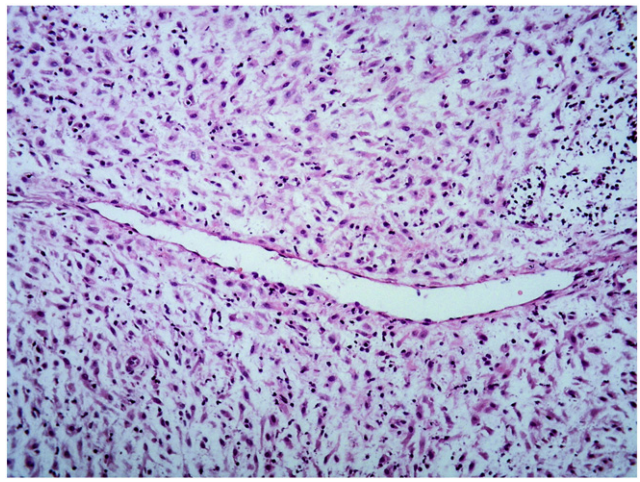

Fig. 4. Progestin (LNG-IUS; Mirena) effect — the stroma shows confluent decidual change. Vessels are thin-walled and ectatic, and clusters of lymphoid cells are present.

6 weeks and 10 weeks of use. At pretreatment, all endometrial biopsies were normal secretory phase. During active treatment, the endometrial histology was as follows: 6 secretory, 4 suppressed, 2 proliferative and 4 could not be dated due to bleeding, from 16 individual participants. There seemed to be a correlation with the endogenous hormonal profile, as normal secretory endometrium was associated with a normal serum progesterone levels [39]. Menstrual disturbances were the principal reason for discontinuation of the method although women with ovulation appeared to have less unscheduled bleeding [18,40].

5. Progesterone receptor modulators

Mifepristone and UPA are PRMs that have been evaluated in menstruating women for contraception and the management of uterine fibroids and endometriosis. These compounds have the potential to be used as long-term contraceptive agents [41]. PRMs bind to the progesterone receptor and elicit tissue specific agonist, antagonist or mixed agonist/antagonist activity. Ligand binding to the progesterone receptor causes dimerization and altered conformation of the ligand-receptor complex, resulting in a unique DNA-binding configuration with subsequent binding of the ligand-receptor complex to the promoter region known as the progesterone response element. Depending on the tissue environment and ligand-receptor complex, recruitment of coregulators, coactivators and coinhibitors results in progesterone agonist or antagonist biologic activity [42].

The interpretation of the endometrial effects of PRMs has varied, from hyperplasia initially to a current consensus that the endometrial changes are specific to the class and do not represent hyperplasia or neoplasia. One study of mifepristone reported a 28% incidence of endometrial hyperplasia, which upon subsequent review was revised to 14% [43–45]. A panel of seven gynecologic pathologists reviewed 84 endometrial specimens from women receiving four different PRMs (mifepristone, asoprisnil, UPA and a Johnson & Johnson compound), including those from the abovementioned mifepristone study. The pathologists were blinded to PRM type, dose, exposure, exposure interval, patient group and indication. The goal was to identify endometrial histologic changes common to PRMs (a "class effect") and to develop consensus terminology and recommendations. The appearance of cystically dilated glands was a frequent architectural finding. Cystic dilation of glands is usually found in proliferative states such as unopposed estrogen effect and hyperplasia, but it is also seen in postmenopausal and inactive states. Glands in the PRM specimens, whether showing cystic dilation or not, had an architecture suggesting proliferative phase, but the glandular epithelial cells were only weakly mitotic and had secretory vacuoles reflecting a progestational stimulus. This discordance of epithelial architecture has been termed a nonphysiologic secretory effect. Other findings included abnormal vasculature (thick-walled and thin-walled blood vessels and anastomosing capillaries). The panel labeled this novel constellation of changes as *PRM-associated endometrial changes* or PAEC. The extent to which PAEC changes are generic to the PRM class or are specific to particular PRM compounds was unclear at that time, and it was acknowledged that more evidence was required to define the endometrial changes [46].

5.1. Mifepristone

Short-term use of mifepristone induces endometrial changes that may contribute to its use as a contraceptive, including regression, retarded development, inhibited glandular secretory activity and decidual necrosis. A study evaluating the effects of 50 mg of mifepristone daily on cycle days 7–10 or 20–23 showed endometrial effects dependent on the time of administration during the cycle. Preovulatory administration resulted in no bleeding episodes during treatment, and the morphology of the endometrium was identical to that found in normal menstruation. In contrast, postovulatory administration resulted in bleeding on the third or fourth day of treatment, and endometrial histology showed early regressive changes corresponding to late postovulatory changes in a normal cycle. Likewise, postovulatory administration induces vascular changes that include capillary endothelial cell necrosis, which may occur without regression of adjacent stroma [47].

Forty-eight percent of women who took mifepristone for 6 months had cystically dilated glands but no evidence of hyperplasia or atypia [48]. A study of mifepristone in doses of 2.5 and 5.0 mg for 6 months for treatment of uterine myomas (fibroids) evaluated the endometrium compared to untreated women. Cystically dilated glands were seen in 86% of endometrial tissue in the treated women and only 4% of untreated women, while few mitotic figures were seen in glandular epithelium, and apoptotic bodies were numerous. Abnormal vessels were variable and seen in 45% of exposed cases. The stroma ranged from compacted cellular to edematous areas, often within the same sample. No endometrial polyps, complex hyperplasia, premalignant lesions, atypical hyperplasia, endometrial intraepithelial neoplasia or carcinoma were noted in any of the samples [21,49].

ZK230211 is a progesterone receptor antagonist that, when administered as an IUS, was shown to induce "estrogenic effects," including tortuous glands, cellular stratification and mitotic activity. The endometrium displayed dilated glands lined by epithelium of secretory morphology, in a background of nondecidualized stroma. The authors noted that, while the findings are consistent with previous results for mifepristone, application of nomenclature used for physiologic processes ("estrogen or progestin-like") may not be justified when dealing with synthetic progesterone antagonists [50].

5.2. Ulipristal acetate

UPA, a PRM in oral doses of 5.0 or 10.0 mg/day, was used to treat women with heavy menstrual bleeding and fibroids in two clinical trials [51,52]. The endometrium after 13 weeks of UPA treatment demonstrated cystic dilation of the glands

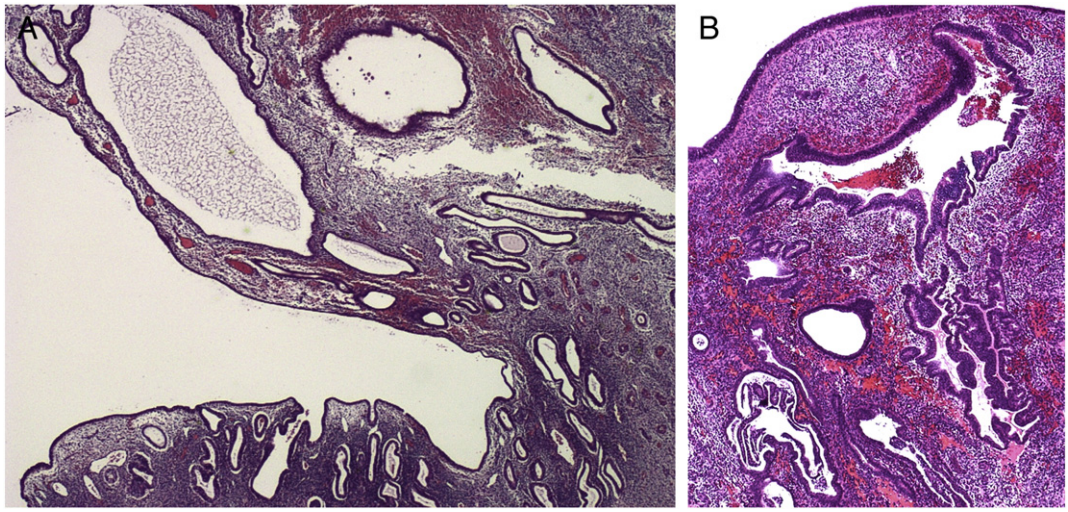

Fig. 5. UPA effect. (A) The endometrial glands show frequent cystic dilatation but have an inactive appearance. Thick-walled arteriolar vessels are present in stroma. The stroma is compact but nondecidualized. (B) Glands have a complex, distorted morphology, sometimes with cystic dilatation. Abortive secretory vacuolation is present. The stroma is compact and nondecidualized with areas of prominent vascularity.

(Fig. 5), similar to other PRMs [53]. The glandular epithelium appeared inactive or contained abortive subnuclear vacuolization and few mitoses. Many glands had a tortuous appearance similar to that seen in the secretory phase. The stroma was of variable cellularity but without predecidual change. Abnormal stromal vasculature was commonly seen, including "chicken-wire" capillaries, aggregates of thickened arterioles and thin-walled ectatic vessels. There was one case of endometrial hyperplasia without atypia and four polyps. Six months after treatment, the endometrium had returned to a normal histologic pattern in the majority of the patients. There was one polyp and no cases of hyperplasia in the UPA-treated groups [53]. These findings indicate that the endometrial changes associated with UPA are reversible upon discontinuation of treatment.

An IVR releasing UPA 600–800 mcg/day for contraception was studied in 37 women. There were no reports of endometrial hyperplasia or cytologic atypia after 12 weeks of use. Inactive endometrium was found in 38% of cases, with widely interspersed tubular glands in a compact stroma. Benign glandular changes described as PAECs were present in 41% of cases [54].

5.3. Summary of endometrial PRM changes

PRMs alter the configuration of the progesterone receptor resulting in endometrial features resembling an unopposed estrogenic effect. This finding of weakly proliferative glandular epithelium might suggest susceptibility to developing endometrial hyperplasia, but to date, this has not been substantiated in the clinical trials. A defining feature of PAECs is relatively inactive appearing endometrium, with low levels of mitotic activity, elevated incidence of apoptosis in the glandular epithelium and compact stroma that is rarely decidualized. The endometrial glandular mitotic activity is low in the PRM-treated women compared to the normal proliferative phase, a consequence of well-recognized but still unexplained endometrial antiproliferative effects of selective progesterone receptor modulators (SPRMs) [55]. There is variation in the pattern of PAEC according to the PRM used, which can be explained by different activities varying from almost pure antagonist effect (e.g., mifepristone) to a mixed agonist–antagonist effect (UPA) [56]. The variability is seen particularly in the nonphysiologic secretory effects, which are frequently prominent with UPA but less common with mifepristone.

6. Conclusion

Exogenous hormones used as contraceptives induce histologic changes with effects on endometrial glandular and stromal architecture, blood vessels and cytology that differ from those that occur during the menstrual ovarian cycle (Table 1).

The common histologic findings with prolonged use of combined oral contraception are atrophy of both glands and stroma and spiral arteriole underdevelopment. There are few morphologic differences between effects of individual progestogenic agents. Injectable contraception with depot medroxyprogesterone induces endometrial changes that include atrophic glands in a background of predecidualized stroma. Intrauterine devices releasing levonorgestrel induce atrophic glands in a background of decidualized stroma and suppression of spiral artery formation with thin-walled dilated vessels. The prominence of such features depends on proximity of the affected endometrium to the device. The IVR with levonorgestrel induces variable secretory and suppressed histologic features that appear to correspond with the hormone profile during treatment. A common feature of all progestin-only contraceptives is the effects on vasculature, in which underdevelopment of spiral arterioles and dilated, thin-walled vessels may contribute to the irregular bleeding common with such contraceptives.

Table 1
Summary histologic changes.

	Duration of therapy	General	Glands	Stroma	Vasculature
E+P	Early — first few cycles	Secretory differentiation, proliferative and secretory features coexist.	S		
	Several cycles	"Pill endometrium"	A	D	Spiral arteriole underdevelopment
	Late	A	A	A	Spiral arteriole underdevelopment
Progestin (systemic)	Early		A	D	Vessels of the superficial endometrium are thin-walled and ectatic
	Late		A	A	Vessels of the superficial endometrium are thin-walled and ectatic
Progestin (local)			Close to IUS: cuboidal-to-columnar epithelium Remote from IUS: flattened cuboidal epithelium	D	Suppression of spiral artery formation and large, thin-walled, dilated vessels
SPRM		PAECs	Cystically dilated	Nondecidualized, compact stroma	Abnormal, three types: dilated, thin-walled, thick-walled, anastomosing capillary

Progestogenic changes — secretory (S), decidualization (D) and atrophy (A).

PAECs include an inactive endometrium with characteristic cystically dilated glands, lined by epithelium with increased apoptosis in a background of compact nondecidualized stroma. Histologic differences between agents appear to depend on the level of antagonism to the progesterone receptor, in which mifepristone does not display the nonphysiologic secretory effect found in UPA. To date, the consensus is that endometrial hyperplasia is not a histologic consequence of PRM treatment.

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