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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].

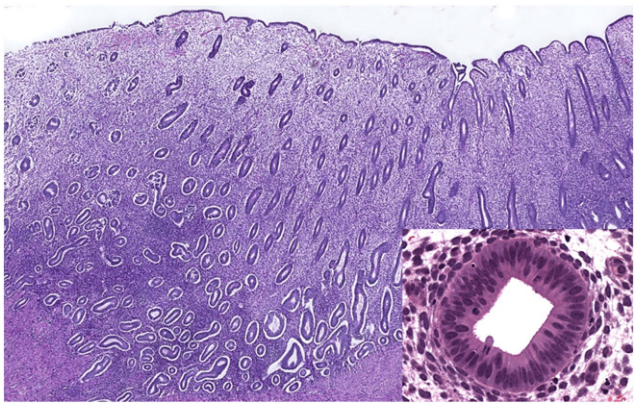

Fig. 1. Proliferative phase: glands are of simple tubular morphology and are evenly distributed in loose stroma. Mitotic activity is widespread in glands (see the inset) and stroma. Inset: proliferative-phase gland.

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.