Physiologic and exogenous hormone effects on the endometrium: important aspects for the surgical pathologist

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Abstract

The endometrium exhibits a unique physiology in its ability to cyclically respond to steroid hormones, resulting in morphologic changes that allow the pathologist's interpretation of proper endometrial function. Distinctive changes are also observed during times of physiologic hormonal changes, such as in pregnancy, or in pathologic and iatrogenic hormonal imbalances, as in certain functioning ovarian tumours and hormone therapy, respectively. The ubiquity of these states, in particular the widespread use of oral contraception, hormone replacement therapy, hormonal intrauterine devices, and nowadays frequent use of progestin as treatment for endometrial hyperplasia and carcinoma, requires that the pathologist be familiar with both the patient history as well as the histologic patterns specific to each entity in order to render an accurate, practical diagnosis for the clinician. Notably, some changes may mimic more worrisome lesions, and vigilance of these similarities and differential diagnosis is necessary in the evaluation of endometrial samples.

Keywords decidualization; endometrium; endometrium carcinoma; exogenous hormone; hyperplasia; IUD; progesterone

Introduction

The endometrium represents the inner glandular epithelial lining of the uterus and provides a nourishing environment for possible implantation of the blastocyst.[1] To fulfil this latter role, the endometrium is unique in that it undergoes cyclical epithelial and stromal morphogenesis during the reproductive years. The spectrum of changes includes an initial proliferative phase, followed by glandular secretion and stromal decidualization, then breakdown and bleeding in the form of menses. The menstrual cycle is a complex physiological phenomenon orchestrated by the release of pituitary follicle stimulating hormone (FSH) and luteinizing hormone (LH) and, in turn, oestrogen (from granulosa cells) and progesterone (from the corpus luteum) in the ovaries. The latter two compounds work directly on the endometrial glands and stroma to facilitate cyclical growth and shedding in physiologic conditions such as menstruation and pregnancy. Variations in the cycle may occur as a result of pathology, as in abnormal uterine bleeding, or iatrogenically, such as with administration of oral contraceptives.

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The normal menstrual cycle

The classical description proposed by Noyes et al.[2] describes in great detail the histologic findings associated with the menstrual cycle. These criteria, however, have come into question, as a recent study[3] found higher variability between fertile women in the number of days of their secretory phase, which was previously thought to be relatively constant. Additionally, interobserver variability was high, leading the authors to conclude that endometrial dating should not be used as a clinical tool in the evaluation of infertility. Although some clinicians may still request dating of their endometrium biopsies,[4,5] most biopsies nowadays are performed for the evaluation of abnormal uterine bleeding[6] and do not require dating. Notwithstanding, accurate dating of the endometrium provides important clinical and pathologic information, such as whether ovulation has occurred or the presence of a lag in the development of secretory glands, i.e. a luteal phase defect, a common cause of dysfunctional uterine bleeding.[7] Endometrial dating, in combination with immunohistochemical staining of uterine natural killer cells, has additionally been proposed to be of prognostic value in women with recurrent reproductive failure for pregnancy outcome.[5] Histologic evaluation can also reveal the presence of polyps, hyperplasia, or neoplasia, which may suggest a possible aetiology of abnormal uterine bleeding.

Based on Noyes' criteria, the cycle begins with menstrual breakdown that lasts 3–4 days, followed by a variable period of proliferation under the primary influence of oestrogen. This is followed by a relatively constant 14-day period of a "normal" 28-day cycle termed as the secretory phase. The day-to-day morphology during the proliferative phase is quite constant, precluding accurate dating during this period. In contrast, morphologic changes during the secretory period are generally reproducible such that one can accurately date the endometrium to within 1–2 days.

Proliferative phase

The proliferative phase is characterized by the endometrium showing small, uniform tubular glands lined by columnar cells with pseudostratified, oval nuclei and small nucleoli. There is brisk mitotic activity both within the glandular epithelium as well as the widely-spaced stromal cells. As the endometrium progresses to the late proliferative phase, the glands become more tortuous and elongated; however, the gland-to-stroma ratio remains constant.

Secretory phase

Following ovulation on day 14, the endometrium enters an "interval phase" in which distinction between proliferative and secretory phase is not possible as characteristics of both are

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present. On day 16, the characteristic morphologic finding is the presence of subnuclear vacuolization of the glandular epithelial cells. These are at first irregularly distributed, even within the same gland, then progressively become more uniform in distribution and migrate upward toward the lumen. By day 18, the secretory vacuoles arrive at the lumen and discharge their contents, thereby distending the glands with clear to slightly eosinophilic mucin peaking by day 20, and ending with secretory exhaustion. The glands at this point often exhibit mild nuclear disarray and a serrated appearance.

Whilst the initial segment of the secretory phase is characterized by glandular changes, the latter portion is defined by changes in the stroma. By day 20, the stroma begins to show oedema with widely-spaced stromal cells, giving the appearance of naked nuclei. The stromal cells then show predecidual change starting on day 23, acquiring a moderate amount of eosinophilic to amphophilic cytoplasm and a polygonal cell shape. These changes first appear around the spiral arteries of the functionalis but then are distributed more regularly. A variable amount of lymphocytes may be present, while the glands are tortuous and compacted.

Menstrual phase

The hallmark of menstrual endometrium is breakdown of the glands and stroma. Stromal cells, having lost their predecidual appearance, are collapsed and tightly packed, resembling "blue balls." Collapsed glands vaguely resemble their appearance during the secretory phase with partially vacuolated cytoplasm. As breakdown progresses, haemorrhage, apoptotic bodies, inflammation, and fibrin deposition are present. Often, small blood vessels show luminal fibrin thrombi.

The endometrium in pregnancy

The underlying drive of the morphologic changes of the cycling endometrium is its sensitivity to the hormones oestrogen and progesterone. In the case of pregnancy, both hormones exert their effects on the uterus via intricate downstream signals to help maintain an environment most suitable for the conceptus.[8] When the ovum is not fertilized, the corpus luteum secretes progesterone, but involution and degeneration to the corpus albicans causes a precipitous fall in progesterone leading to menstruation. To maintain secretion of progesterone and thus the pregnancy, human chorionic gonadotropin is secreted by the syncytiotrophoblasts of the newly-developed blastocyst.[9] After the eighth week of pregnancy, the placenta begins secretion of oestrogen and progesterone, the latter of which leads to decidualization of the endometrial stromal cells. This differs from the secretory phase predecidua in that true decidual cells acquire even more eosinophilic cytoplasm, have round nuclei, and obtain prominent cell borders.[10] In early pregnancy, glandular changes are not much different than those of the late secretory phase, with glandular dilation, variable epithelial vacuolization and often a serrated appearance. The persistence of vacuolization as compared to the late secretory phase may be one clue to the presence of an early pregnancy. Practically, however, the morphologic distinction is often difficult until after 2 weeks of conception, when the glands may show atrophic change. Not uncommonly, the glands may be more architecturally complex, with papillary formations consisting of bland epithelium exhibiting low mitotic activity. Rarely, the nuclei may be optically clear. This change is attributed to biotin accumulation and may resemble cytomegalovirus or herpes simplex virus infection.[11] The spiral arteries become more prominent, with acquisition of thicker walls. Intimal proliferation of myofibroblasts within the vessel wall, and presence of foam cells are proposed to be an indication of intrauterine pregnancy. Dilated venules may be present under the surface epithelium.

Arias-Stella reaction

An important glandular change that is often seen in both intrauterine and ectopic pregnancies is the Arias-Stella reaction. This change occurs between 4 and 8 weeks after implantation and is a physiologic glandular response to the presence of trophoblastic tissue. The glands often become hypersecretory with prominent vacuolization of the cytoplasm and characteristic nuclear hyperchromasia, "hobnailing", stratification, enlargement and, occasionally, intranuclear cytoplasmic invaginations. Mitotic activity is uncommon with a generally low MIB-1 index. The Arias-Stella reaction may be present focally in just a few glands or be evenly distributed throughout the endometrium, and can persist up to 8 weeks following delivery.

Various morphologic variants have been recognized: minimal atypia (showing mild nuclear enlargement), secretory (resembling day 17 secretory endometrium), hypersecretory (the classic/usual form with diffuse cytoplasmic vacuolization), nonsecretory (resembling proliferative glands with vesicular chromatin in glandular nuclei), and monster cell (with bizarre, enlarged nuclei involving the entire gland).[12] The significance of the Arias-Stella reaction is its morphologic similarity with various neoplasms, particularly clear cell carcinoma, both of which can show nuclear enlargement, hobnail-shape, and atypia. A clinical history of concurrent or recent pregnancy favours Arias-Stella reaction. Morphologically, the presence of decidua, low nucleus to cytoplasm ratio, low mitotic activity, lack of stromal invasion, and absence of a mass lesion are all features of Arias-Stella reaction that argue against the diagnosis of clear cell carcinoma.

Uncommonly, the Arias-Stella reaction can be seen in the fallopian tube, cervical epithelium, or involve endometriosis.[13,14] Again, clues to the diagnosis would be history of concurrent or recent pregnancy or the use of hormonal agents. Rarely, however, the Arias-Stella reaction can be seen in post- or perimenopausal women without pregnancy,[15] likely due to effects of administered exogenous progestins.

Ectopic pregnancy

Endometrial changes may occur whether the pregnancy is intrauterine or ectopic. Thus, the features of gestational endometrium and/or the Arias-Stella reaction are not sufficient to diagnose an intrauterine pregnancy. The presence of trophoblastic tissue in the form of chorionic villi or placental implantation site, defined as intermediate trophoblasts invading the decidualized endometrium, is required.

Hormone-producing tumours and their effects on the endometrium

Hormone-secreting tumours, particularly oestrogenic ovarian tumours, will lead to characteristic changes in the endometrium.

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