

Common Hormone and Drug Induced Changes on Endometrial Morphology

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ABSTRACT

The endometrium is a tissue that has a varied and changing morphological patterns with changes due to normal physiological and cyclical processes over the life span of women. In addition the morphological changes produced due to hormones, exogenous, endogenous and drugs are complex and paradoxical at times making interpretation a challenging job for pathologists. A discussion is made in this context in this article.

Keywords: Endometrium, Infertility, Drugs, hormones

INTRODUCTION

The endometrial tissue is a dynamically changing tissue in response to various hormonal effects. A discussion is made on the effects due to hormones and the histological changes that occur after administration of exogenous hormones for various clinical conditions affecting women of reproductive age group and thereafter.

The morphological changes by these drugs are overlapping in nature and are a challenging one for interpretation. The patterns seen on morphology do not fit the routine changes that are seen in a hormonal endometrium. Often confusing, overlapping patterns are seen and without history and clinical details it becomes even more difficult to interpret. In spite of all these factors, certain patterns are seen which can be recognized and documented.

EXOGENOUS HORMONAL EFFECTS

Hormonal agents are given to prevent a pregnancy by a simulatory mechanism, that presence of one pregnancy prevents onset of another. The end result is that there is suppression of ovulation and implantation.

The classical OC was in the form of sequential or combined regimen. The former mimics the natural cycle Weekly estrogens are administered during first 5-19 days. After that progesterone is given upto 24th day which after stopping leads to withdrawal bleeding. This regimen is no longer used as it led to many cases of endometrial hyperplasia. Other side effects were also seen like increase in incidence of thromboembolism.¹

The effect on endometrium due to these hormones is endometrial stromal cell hyperplasia, decidualization and glandular atrophy. Now-a-days, doses of estrogen and progesterone are reduced in dosage. Initially there is glandular proliferation with slightly coiled glands lined by immature epithelial cells. The typical proliferative changes seen in the form of stratification and mitotic activity is characteristically

absent. Vacuoles which may be sub or supra nuclear are seen in no definite pattern.²

The glands are distributed within the stroma in uneven pattern with varying distance between the glands. More commonly, a decidual reaction is seen in the stroma. The spiral arterioles do not show the characteristic changes which appear to be dilated and even thrombosed.

OVULATION INDUCTION THERAPY

In this age of even increasing number of infertile couples, ovulation failure is seen in around 20-30% of infertile women. There is a deficiency of gonadotrophins which results in deficient follicle maturation.

For in vitro fertilization, ova has be retrieved which is done by hyperstimulation of ovaries. The drugs used are clomiphene citrate, gonadotrophin releasing hormone and human chorionic gonadotrophins. In these regimens there is an acceleration of secretory changes in the stroma. There an advanced stromal maturation and less advanced glandular maturation. The glands display early secretory changes in the form of subnuclear vacuoles of days 16 or 17 with stromal changes of day 22-23. Atypical glandular hyperplasia, endometrial hyperplasia and even endometrial carcinoma has been reported in patients treated for ovulation induction for PCOD.

POST REPRODUCTIVE AGE GROUP

These patients are prescribed hormonal agents in their post-menopausal years for alterations of many symptoms accompanying decline in natural hormones. Used alone, estrogen alone lead to an increase in cases of endometrial hyperplasia and neoplasia.³ This is the reason that both estrogen and progesterone are used in hormone replacement therapy. In these regimens, the doses of the hormones have been reduced significantly. The progesterone is added in the last 10 days of the cycle.⁴

The endometrium shows proliferative endometrium or weakly proliferative activity in unopposed estrogen therapy.

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Hormonal Oral Contraceptives	Tamoxifen GnRH Agonists
Glandular proliferation arrest	Glandular atrophy
Abortive secretion	Stromal hyperplasia
Low gland/stroma proportion	Pseudosarcoma
Stromal edema	Vascular thickening
Decidualization	Stromal leiomyomas
Dilated blood vessels,	
Atrophic glands	

Table-1: Endometrial Histology in Oral Contraceptive Therapy

Other changes include stromal breakdown with endometrial hyperplasia ranging from simple to complex and atypical. Metaplastic changes can also be seen. There is also increase in the incidence of endometrial polyps. Endometrial carcinoma can also occur over a prolonged exposure of estrogen.⁵

Combined therapy of hormones shows weakly to intensely proliferative or secretory changes with sub or supranuclear vacuoles and luminal secretion. Metaplastic changes in the form of eosinophilic, mucinous or papillary changes are seen. There may be supra-added menstrual changes in the form of stromal breakdown, fibrinoid intravascular thrombi and cellular debris.⁶

There can be a combination of inactive or atrophic endometrium with few areas showing functional or hyperplastic changes. These changes overlap with endogenous hormone production in post menopausal women whereby a combination as described above can be seen. Neoplastic changes are prevented by addition of progesterone to estrogen therapies.^{6,7,8,9}

ANTI-NEOPLASTIC HORMONE THERAPY

Progesterone is used for the treatment of endometrial hyperplasia. It is also given in endometrial carcinomas. There is arrest of glandular proliferation with secretory changes in the glands and decidualization of stroma. There is no or minimal mitotic activity. There is little architectural changes in the endometrium.

Gonadotrophin releasing hormone agonists are used to reduce the size of uterine leiomyomas by simulating a menopause which is reversible due to decreased estrogenic stimulation.¹⁰ There is shrinkage in the size of leiomyomas. The changes that are seen are edema or necrosis during first weeks followed by modular hyalinization and occasional lymphoid cell infiltrates. The endometrium shows weakly proliferative activity and in time becomes atrophic.

Tamoxifen is used for adjuvant therapy and prophylaxis of breast cancer. It has an antiestrogen effect on the breast tissue. On the uterus it has both agonistic as well antagonistic action towards estrogens.¹¹

Due to its agonistic actions there is endometrial proliferation with hyperplasia of a wide range. A classic finding is a polyp of which stroma is densely fibrotic. There is also myometrial proliferation includes multiple leiomyomas and foci of Adenomyosis. The size of uterus also increases, sometimes considerably. Metaplastic changes like mucinous metaplasia

is also observed. Endometrial carcinoma was seen in 10 cases. Out of 277 patients well differentiated endometroid carcinoma was seen in 5 cases confined to polyps whereas 5 cases shows less differentiated carcinomas. Carcinosarcomas were also seen which are difficult to assess.^{12,13,14,15}

CONCLUSION

Hormonal treatment regimens are widely used throughout the globe for various reasons. These reasons include oral contraception to hormone replacement in menopausal age group. Also included are those women amongst the infertility group. A smaller group is of those women who receive adjuvant therapy for tumours of breast and uterus.

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