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Research Article

A Study to Correlate Endometrial Hyperplasia with Ovarian Stromal Change

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Abstract

Background: Endometrial hyperplasia in peri-menopausal age group is frequently encountered as a result of unopposed excess estrogen action, exact source of which is still debatable. Possible source is ovarian stroma. There must be some subtle changes in ovarian stroma to produce excess estrogen in such states. This study was performed to provide new insights into the various patterns of subtle ovarian stromal changes and its relation to morphological alteration of endometrial glands and stroma.

Methods: 62 women in peri-menopausal age group, diagnosed as endometrial hyperplasia on uterine curettage and unresponsive to conventional therapy, treated by total hysterectomy with unilateral/bilateral salpingo-oophorectomy, were chosen randomly. Serial step sections of endometrial biopsies were examined by routine microscopy. Endometrial hyperplasia was classified following the current WHO classification. The sections from the ovary were examined for changes in the ovarian stroma.

Results: Out of the 62 total cases having endometrial hyperplasia, 53 cases (83.5%) had one or more subtle ovarian stromal changes and 9 cases (14.5%) lacked the ovarian stromal changes. Out of the 50 cases without endometrial hyperplasia, only eight had subtle ovarian changes. In the 53 cases, which showed ovarian stromal changes, the changes were found in combination and variable proportions.

Conclusion: Ovarian stromal changes were significantly associated with endometrial hyperplasia.

Keywords: Endometrium, Hyperplasia, Ovary, Stroma

Introduction

Endometrial hyperplasia is defined as endometrial thickening with a proliferation of irregularly sized and shaped glands and an increased gland-to-stroma ratio.[1]

Hyperplasia develops as a result of unopposed estrogenic stimulation, and consequently most patients with hyperplasia have a history of either persistent anovulation or exogenous unopposed estrogen therapy.[2,3] On the contrary, endometrial hyperplasia in peri-menopausal age group is frequently encountered as a result of unopposed excess estrogen action, exact source of which is still debatable. Possible source is ovarian stroma. There must be some subtle changes in ovarian stroma to produce excess estrogen in such states.

The diseases are mostly self-limited and are mostly treated with progestagens, which was previously termed as 'chemical currettage'. But some of them progress to atypical hyperplasia, which is considered as a precursor lesion to endometrial adenocarcinoma, as well as some hormone-nonresponders require abdominal hysterectomy with unilateral/bilateral salpingo-oophorectomy as a part of their treatment protocol. Patients with a diagnosis of atypical hyperplasia can be treated with progestins or a

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hysterectomy. Nearly 60% of atypical hyperplasias regress, but the likelihood of residual carcinoma in the uterus after a curettage increases with age.[4,5]

Few studies described ovarian changes, associated with endometrial hyperplasia. This study was performed to provide new insights into the various patterns of subtle ovarian stromal changes and their relation to morphological alteration of endometrial glands and stroma.

Materials and Methods

Sixty-two women in peri-menopausal age group, diagnosed as endometrial hyperplasia on uterine curettage and unresponsive to conventional therapy treated by total hysterectomy with unilateral/bilateral salpingo-oophorectomy, were chosen randomly. Also 50 cases, which had had total hysterectomy and salpingo-oophorectomy for causes other than endometrial hyperplasia or malignancy, were selected

Cases with endometrial pathology other than endometrial hyperplasia such as endometrial carcinoma and those with history of exogenous estrogen therapy were excluded.

Study Design

A descriptive, observational, cross-sectional study.

Method of Data Collection

Serial step sections of endometrial biopsies were examined by routine microscopy.

Multiple sections from the endomyometrium at 1 cm interval from the total hysterectomy specimens previously diagnosed as endometrial hyperplasia were done. The whole ovary/ovaries was processed in multiple slices.

Hematoxylin and Eosin staining of sections from paraffin blocks of ovary and endomyometrium along with special stains, if necessary, was done.

The stained slides were evaluated for different changes in the ovarian stroma.

Histopathological parameters studied in endometrial biopsy (Curettage material) and sections from endometrium were as follows:

- Pattern of distribution of endometrial gland and stroma
- Gland and stromal ratio
- Architecture of endometrial glands
- Lining of endometrial glands
- If there is any nuclear stratification or not.
- To note any obvious mitotic activity.
- If there is presence of any nuclear atypia or not.
- Architecture of stroma.
- If there is pseudodecidual or any other changes in stroma.
- Endometrial hyperplasia is defined as a proliferation of glands of irregular size and shape with an associated increase in the gland/stroma ratio compared with proliferative endometrium. Current classification of WHO 2014 was followed:

1. Atypical hyperplasia.
2. Hyperplasia without atypia

Histopathological parameters studied in sections from ovaries were as follows:

- Stromal cellularity.
- Stromal edema.
- Ovarian stromal hyperplasia was defined as diffuse or nodular proliferation of plump ovarian cortical stromal cells encroaching on the medulla.
- Cystic changes of follicles/follicular cyst (normal follicle measures up to 1 cm in greater dimension, while follicular cysts measure 2.5 to 10 cm in diameter and contain serosanguineous fluid/corpus luteal cyst (the cyst has an undulating wall of luteinized granulosa cells that have abundant eosinophilic cytoplasm).
- Degree of stromal thecosis or luteinization of stroma as observed per estimated high power field, compared to normal ovary (graded on subjective evaluation). The nuclei of stromal cells are enlarged and their chromatin condenses into coarse granules. Instead of a small, dark staining, spindle-type of cells, large, plump, pale staining cell resembling lutein cells are seen.
- Presence of any abortive follicle.
- Interstitial glands or surface inclusion cysts. Inclusion cysts measure less than 1 cm in diameter. The cysts are lined by a single layer of bland flat, cuboidal, or ciliated columnar cells.
- Presence of any tumor tissues with their morphological description.
- Presence of any ovarian cysts and their lining epithelium.

Statistical Analysis

All numerical data were compared by using 2-tailed t-test and all the categorical data were compared by using Chi-square test. For statistical significance, p-value of less than 0.05 was considered. Statistical analysis was done by using SPSS software, version 20.

Results

Among 62 patients with endometrial hyperplasia, 14% (9 patients) were below 40 years, 10% (6 patients) were within the age group of 40 to 45 years, 20% (12 patients) were within the age group of 46 to 50 years, and the rest 56% (35 patients) were in the age group of above 50 years (Table 1).

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Table 1.Percentage Distribution of Patients in Different Age Groups (n=62)

Age	Number	Percentage
<40	9	14
40–45	6	10
46–50	12	20
>50	35	56

Among 62 patients, 61% (38) had features of simple hyperplasia without atypia; 3% (02) had features of simple hyperplasia with atypia; 14 had features of complex hyperplasia without atypia; and 13% had features of complex hyperplasia with atypia (Table 2). Among 50 cases without endometrial hyperplasia, 35 had uterine myoma, 10 had adenomyosis and 5 had genital prolapse.

Table 2.Distribution of the Different Types of Hyperplasia and Subtle Ovarian Changes

	Without Atypia	With Atypia
Simple Hyperplasia	38	2
Complex hyperplasia	14	8
Ovarian changes	45	8

Out of the 62 total cases having endometrial hyperplasia, 53 cases (83.5%) had one or more subtle ovarian stromal changes and 9 cases (14.5%) lacked the ovarian stromal changes. Out of the 50 cases without endometrial hyperplasia, only eight cases had subtle ovarian changes (Table 3). Ovarian stromal changes were significantly associated with endometrial hyperplasia.

Table 3.Ovarian Changes Are Significantly Associated with Endometrial Hyperplasia

	Ovarian Change	No Ovarian Change
Endometrial hyperplasia	53	9
No endometrial hyperplasia	8	42

Ovarian changes are significantly associated with endometrial hyperplasia ($p<.05$ by Chi-square test).

In the 53 cases, which showed ovarian stromal changes, the changes were found in combination and variable proportions. 53.2% (33 cases) showed non-specific stromal hyperplasia, 72.6% (45 cases) showed stromal luteinization, 6.5% (4 cases) showed stromal thecosis, 8.1% (5 cases) showed polycystic changes and focal granulosa cell hyperplasia, 32.3% (20 cases) showed presence of interstitial glands and 14.5% (9 cases) showed follicular cyst formation (Table4).

Table 4.Percentage Distribution of Subtle Ovarian Stromal Changes in Otherwise Normal Ovaries (on Oophorectomy Specimens)

Subtle Ovarian Changes	Number of Cases	Percentage of Cases
Non-specific stromal hyperplasia	33	53.2
Luteinization of stroma	45	72.6
Thecosis of stroma	04	6.5
PCOS and focal granulosa cell hyperplasia	05	8.1
Interstitial glands.	20	32.3
Follicular cyst	09	14.5

Out of 10 cases of endometrial hyperplasia with atypia, eight cases showed ovarian stromal changes while out of 52 cases of endometrial hyperplasia without atypia, 45 cases showed ovarian stromal changes. Endometrial hyperplasia with atypia is not significantly associated with ovarian stromal change.

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Discussion

In this study, the cases of endometrial hyperplasia were within the age range of 39 to 57 years with a predilection for 50 years (56%) and above. Reed et al.[6] showed that the incidence of endometrial hyperplasia with or without atypia peaks in the early postmenopausal years and in the early 60s, respectively. In the study of Ricci[7] et al., epidemiologic characteristics of endometrial hyperplasia in women aged 35–73 (median 51 years) was analyzed.

Most of the cases in this study (83.5%) showed the subtle ovarian stromal changes in cases of different types of endometrial hyperplasia with or without atypia, indicating that various stromal changes in various combinations and different proportions may be a reason behind unopposed hyperestrogenic state in cases of endometrial hyperplasia. No definite correlation was, however, observed regarding presence or absence of atypia and ovarian stromal changes.

Various studies have shown independent ovarian stromal change in correlation to hyperestrogenic state. Cheung,[8] Holm,[9] and Marshall[10] studies have shown that PCOS may be significantly associated with an increased risk of endometrial hyperplasia. Farber et al.,[11] Aiman et al.,[12] Turunen,[13] Sluijmer et al.,[14] Sasano et al.,[15] and Lawrence[16] also studied ovarian stromal cells and their luteinization and told that increase functional activity of luteinized stromal cells often produces significant quantities of steroid hormones. Mossman[17] and Zheleznov et al.[18] in their studies also told that there was no significant association between interstitial glands and estrogen. In our study, a combination of stromal changes, not a single factor was a factor in predicting the etiology of endometrial hyperplasia. Non-specific stromal hyperplasia was the commonest observation among different subtle changes. The comatosis, luteinization of stroma, islets of granulosa-lutein cells, interstitial glands, polycystic ovary, etc., were the other different observations, either singly or in combination. We found that simple endometrial hyperplasia without atypia is the commonest entity to produce uncontrolled meno-metrorrhagia leading to hysterectomy.

This study was conducted on low-risk population having poor socio-economic status without any family history of endometrial adenocarcinoma, epithelial neoplasm or any other significant medical illness. Also, this is a tertiary hospital-based study having very short period and limited cases, and therefore biased result is possible.

Larger population-based study covering moderate to high-risk population along with different strata of population may reveal different results. Low sample size may be an independent factor for fallacy.

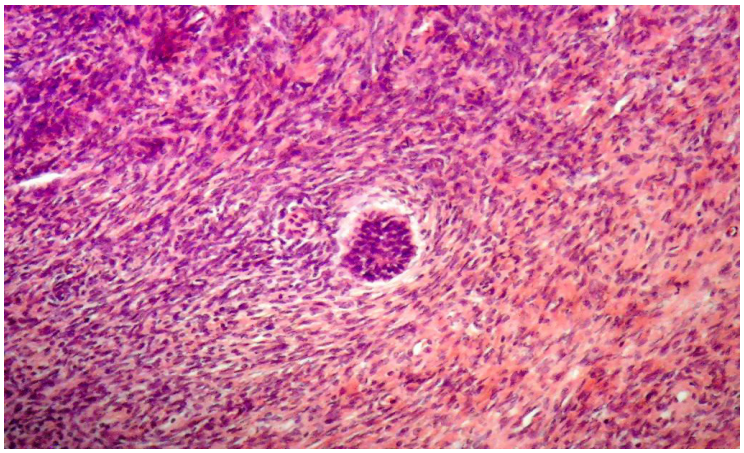

Figure 1.Non-specific Stromal Hyperplasia (H&E, X40)

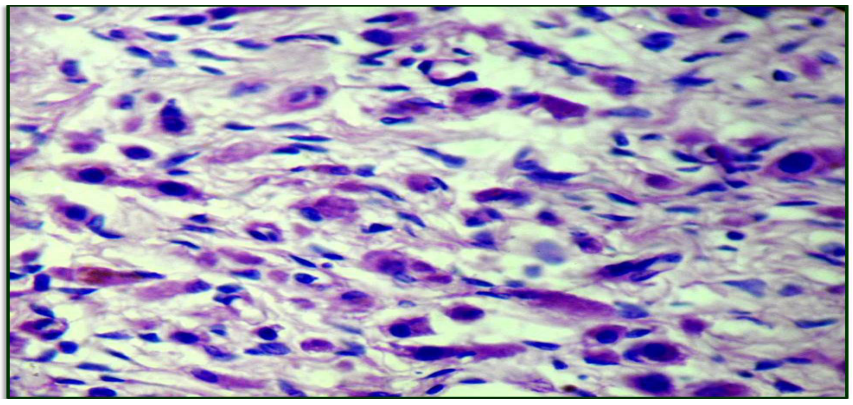

Figure 2.Luteinization of stroma (H&E, X40)

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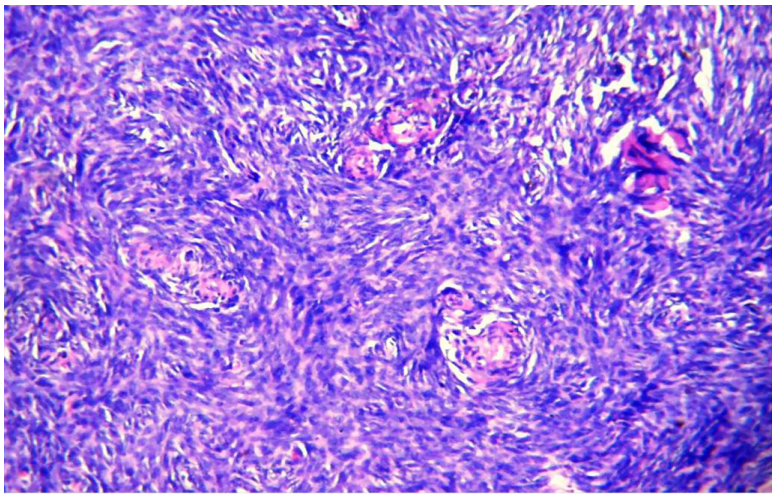

Figure 3.Interstitial Glands in Ovarian Stroma (H&E, X40)

Conflict of Interest: None

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