ORIGINAL ARTICLE

Endometrial Histology in Epithelial Ovarian Tumors: A Critical Analysis

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Abstract

Objective: The aim of the present study is to determine the prevalence of abnormal endometrial histology, premalignancy, and malignancy in women diagnosed with epithelial ovarian tumors and tumor-like conditions (PCOS, endometriosis, stromal hyperplasia, and stromal hyperthecosis).

Materials and methods: Endometrial and ovarian specimens of 71 patients with epithelial ovarian tumors were retrospectively selected, and the histopathology was analyzed. Moreover, 79% had serous tumors, 15.4% had mucinous tumors, and 5.6% other tumors (fibrothecoma, cystadenofibroma). Ovarian histopathology was compared with the concurrent endometrial pathology.

Results: Among the samples analyzed, 41% had abnormal endometrial histology, of which 29% is polypoidal endometrium and 12% is disordered proliferation, both of which represent hyperestrogenic state.

Conclusion: Abnormal endometrial histology due to stromal steroidogenesis and its biological action on endometrium is well-known; hence, endometrial evaluation is mandatory for planning treatment and understanding the disease process of epithelial ovarian tumors.

Keywords: Bioactive E2, SF-1, Stromal steroidogenesis.

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Introduction

Ovarian tissues are constantly in a dynamic state even before puberty and after menopause, which are under the action of gonadotropins and have got steroidogenic potentialities. Contrary to the popular belief that epithelial ovarian tumors are nonhormone secreting, stromal steroidogenesis of the epithelial ovarian tumors has been proved by various studies. (1) Increased expression of sex steroid differentiation and steroidogenesis in epithelial ovarian tumors. (2) The expression of (a) stromal steroidal enzymes involved in hormone biosynthesis (CYP17, CYP19, HSD17beta, AKR1c3), (b) immunohistochemical markers (calretinin, inhibin, steroidogenic factor-1SF-1), and (c) hormone receptors (estrogen, progesterone, and androgen receptors) by the epithelial ovarian tumors and the estrogen synthesis by these. (3) Ovarian stroma is biologically active and has an effect on bone metabolism and abnormal endometrial histology. (4) The increased estrogen secretion proved by estimating the increased level of estrogen in the ovarian vein draining the ovarian tumor comparing the contralateral ovarian vein. Therefore, in the present study, we evaluated the endometrial pattern of the patients who were diagnosed to have epithelial ovarian tumors (benign and malignant) ultimately which may influence the plan of treatment.

Materials and Methods

This is a retrospective observational study conducted in Sri Ramachandra Institute of Higher Education and Research Institute (January 2017–April 2019). Seventy-one cases were selected who were operated for epithelial ovarian tumors (cystectomy/hysterectomy). The histopathology of the ovarian tumor and endometrium was analyzed. The results were tabulated and analyzed.

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Results

Table 1: Among the 71 samples analyzed, 79% had serous tumors, 15.4% had mucinous tumors, and 5.6% had other tumors. Among the 71 samples, 41% had abnormal histology, of which 29% had polypoidal endometrium and 12% had disordered proliferation.

Table 2: In the premenopausal age-group (49 samples), 88% had serous tumors and 12% had mucinous tumors, and 44.8% had abnormal endometrial histology, of which 30.6% is polypoidal endometrium and 14.2% is disordered proliferation.

Table 3: In the postmenopausal age-group (22 samples), 59% had serous tumors, 22.4% had mucinous tumors, and 13.6% other tumors. Among 22 samples, 45% had abnormal endometrial histology, 22.7% had polypoidal endometrium, 13.3% proliferative pattern, and 9% disordered proliferation. Proliferative pattern in postmenopausal women indicates hyperestrogenic state which is why it is considered as an abnormal endometrial histology.

Table 1: Ovarian and endometrial histopathalogy in age-group (*N* = 71)

Ovarian histopathology (N = 71)	*Endometrial histopathology (N = 71)*
Benign serous cyst (*n* = 55)	Polypoidal endometrium (*n* = 18), Proliferative pattern (*n* = 16), Disordered proliferative pattern (*n* = 6), Endometrium unremarkable (*n* = 4), Regressive cystic change (*n* = 1), Secretory pattern (*n* = 4), Atrophic pattern (*n* = 6)
Benign seromucinous cystadenoma (*n* = 1)	Atrophic pattern (*n* = 1)
Benign mucinous cystadenoma (*n* = 6)	Proliferative pattern (*n* = 4), Disordered proliferation (*n* = 1), Endometrium unremarkable (*n* = 1)
Borderline mucinous tumor (*n* = 5)	Regressive cystic change (*n* = 2), Disordered proliferation (*n* = 1), Benign endometrial polyp (*n* = 1), Proliferative pattern (*n* = 1)
Noninvasive serous CA (*n* = 1)	Secretory pattern (*n* = 1)
Serous fibrothecoma (*n* = 1)	Disordered proliferation (*n* = 1)
Cystadenofibroma (*n* = 2)	Endometrial polyp (*n* = 1), Regressive cystic change (*n* = 1)

Table 2: Ovarian and endometrial histopathology in premenopausal age-group (*N* = 49)

Ovarian histopathology	*Endometrial histopathology*
Serous cystadenoma (*n* = 42)	Polypoidal endometrium (*n* = 15)
Noninvasive serous CA (*n* = 1)	Disordered proliferation (*n* = 7)
Borderline mucinous (*n* = 2)	Secretory pattern (*n* = 5)
Benign mucinous (*n* = 4)	Proliferative pattern (*n* = 18)
	Endometrium unremarkable (*n* = 4)

Table 3: Ovarian and endometrial histopathology in postmenopausal age-group (*N* = 22)

Ovarian histopathology	*Endometrial histopathology*
Serous cystadenoma (*n* = 13)	Polypoidal endometrium (*n* = 5)
Benign mucinous (*n* = 2)	Disordered proliferation (*n* = 2)
Fibrothecoma (*n* = 1)	Endometrium unremarkable (*n* = 1)
Cystadenofibroma (*n* = 2)	Atrophic endometrium (*n* = 7)
Benign seromucinous cystadenoma (*n* = 1)	Proliferative pattern (*n* = 3)
Borderline mucinous (*n* = 3)	Regressive cystic change (*n* = 4)

Discussion

A study on steroid hormone synthesis by ovarian stroma has been carried out with the hypothesis that ovarian stroma immediately adjacent to the tumor expresses matrix of sex steroid differentiation, steroidogenesis, and steroid enzymes, whereas epithelium contains corresponding hormone receptors. Non-sexcord stromal tumors and tumor-like conditions express steroidal enzymes involved in hormone biosynthesis (CYP17, CYP19, HSD17beta, AKR1c3), immunohistochemical markers of sex steroid differentiation and steroidogenesis (calretinin, inhibin, and steroidogenic factor 1), hormonal receptors (estrogen and progesterone receptors).[1]

A study on ovarian stromal steroidogenesis explains the presence of SF1, which is a master regulator of steroidogenesis that induces the differentiation of mesenchymal cells into steroidogenic cells in women with common epithelial tumors. Overexpression of SF1 in these tumors regulates P450 aromatase, which promotes estrogen biosynthesis which in turn induces increased serum E2 level, and the estrogen secreted from these tumors has biological activity.[2]

A study on postmenopausal women with non-sexcord stromal tumors showed increased estrogen-producing activity of common epithelial tumors and metastatic ovarian tumors by the following findings: (1) High preoperative E2 levels which decreased to normal after complete resection but returned to abnormal range following recurrence. (2) Higher E2 levels were detected in ovarian vein draining the tumorous ovary than in peripheral or contralateral ovarian vein. (3) Steroidogenesis-related enzymes were found to localize in the tumor cells. The striking fact is that E2 released from these tumors has biological effects on bone and endometrium, which was supported by (1) Decreased urinary levels of N-telopeptide of type 1 collagen and decreased bone-specific alkaline phosphatase in high E2 group. (2) Decreased bone mineral density after surgery. (3) The prevalence of abnormal endometrial histology was 6.7% in postmenopausal women with non-sexcord stromal ovarian tumors including four patients (5.3%) with grade 1 endometrioid carcinoma. Prevalence of endometrial carcinoma was higher than prevalence in general population. Therefore, they concluded that E2 released from non-sexcord stromal tumors has biological effect on incidence of abnormal endometrial histology. However, they also opined endometrial tumors share a lot of common etiological factors with ovarian tumors. These factors may also contribute to abnormal endometrial histology.[3]

An MRI study showed that surface epithelial tumors are the most common type to have estrogenic stroma. Many ovarian tumors and tumor-like conditions produce estrogen and androgen. MRI can demonstrate not only characteristics of ovarian tumor but also an enlarged uterus size with thick endometrium even in cases of clinically latent excess of estrogen. They also state that epithelial ovarian carcinoma, especially mucinous neoplasms, has estrogenic stroma, which can present with increased endometrial thickness and uterine bleeding. Androstenedione produced by the hyperplastic stromal cells of the ovary containing the mucinous cystadenoma gets converted into estrone, resulting in massive increase in endogenous estrogen formation and endometrial hyperplasia.[4]

A study on postmenopausal women states that androstenedione from adrenals is converted to estrone in adipose tissue using aromatase and the conversion increases with age. Hence, the postmenopausal endometrium that can be atrophic or with cystic change can show weak proliferative activity resulting in endometrioid carcinoma or hormone-dependent ovarian carcinoma, which warrants our attention to look for whether atrophic endometrium is active or inactive in the histopathology.[5]

BMJ case reports published online in June 2013 reported association between large functional benign endometrioid cystadenofibroma of ovary leading to endometrial cystic glandular hyperplasia and postmenopausal bleeding.[6]

A study published in 1981 stated that estrogen excretion was higher than normal in benign and malignant epithelial tumors of ovary, endometrioid, and metastatic tumors.[7]

Article published in AJCP in 2014 stated that there is high prevalence of atypical hyperplasia in the endometrium of patients with epithelial ovarian carcinoma especially endometrioid ovarian tumor and also in one-fourth of the patients with serous ovarian carcinoma.[8]

Estrogen-producing activity of common epithelial tumors (54 cases) and metastatic tumors (4 cases) of the ovary was clinically and endocrinologically studied in postmenopausal patients. High serum concentrations of E1 (greater than or equal to 50 pg/mL) and E2 (greater than or equal to 30 pg/mL) were demonstrated in 78% in the group of postmenopausal patients. The increased estrogen was reflected in such target tissues as the endometrium and vaginal mucosa. Proliferation, hyperplasia, atypical hyperplasia, and even a case of carcinoma of the endometrium were observed in patients with ovarian tumors. An increase in the karyopyknotic index (KPI) of the vaginal smear, as well as uterine bleeding, could be an important sign of asymptomatic ovarian tumors in postmenopausal women.[9]

Article published in BJC in 2016 demonstrated a striking similarity between the protein expression profiles of ovarian and endometrial high-grade serous carcinoma and also noted similar gene expressions in renal, endometrial, and ovarian clear cell carcinoma. Several studies showed that there are similar risk factor profiles and several common genes and pathways involved in the molecular pathogenesis of endometrial and ovarian carcinoma. Serous tumors are characterized by defects in P53 and endometrioid tumors associated with PTEN or beta-catenin mutation, regardless of organ of origin.[10,11]

Association of abnormal endometrial histology in a patient with epithelial ovarian tumors in both premenopausal and postmenopausal women has been established beyond doubt. While planning for conservative (cystectomy) treatment, abnormal endometrial histology should be ruled out. Abnormal endometrial histology also helps to decide on whether simple or radical approach is needed for management.[12,13]

Conclusion

In the present study, most of the cysts though benign were found to be associated with endometrial pathology such as polypoidal endometrium, which represents hyperestrogenic state, and as per the literature, most of the benign and malignant epithelial ovarian neoplasms, PCOS, and endometriosis are all associated with endometrial pathologies due to hyperestrogenism contrary to the old belief hyperestrogenism is consistent only with sexcord stromal tumors. The correlation between endometrial pathology and ovarian tumors has been proved beyond doubt. This emphasizes the fact that endometrial evaluation is mandatory for a patient with ovarian tumor, irrespective of age and size. In our analysis, sample size is small. A larger sample size with more readily available endometrial samplings for all patients can predict a better outcome and better correlation.

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