Research Paper

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A Study of Endometrial Pathology in Abnormal Uterine Bleeding in Peri Menopausal and Post Menopausal Patients of Kanchipuram District

Medical Science

KEYWORDS : Uterine bleeding, Proliferative, Secretory, Hyperplasia, Endometrium

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ABSTRACT

Introduction:

The endometrium is the sheet of cells that grows monthly to line the uterus. Normally, women naturally expel these endometrial cells during menstruation. In some women, however, the growth of cells becomes excessive, resulting either in flat or protruding growths, called endometrial polyps, or in a thickening of the endometrium, called endometrial hyperplasia. Hyperplasia can lead to cancer if not treated. These conditions may occur when a woman's hormone levels are out of balance as her endocrine glands produce too much estrogen and not enough progesterone-like hormones that would normally work to counteract estrogen's tissue-producing properties. Aim:To evaluate Endometrial pathology in abnormal Uterine bleeding in peri and post menopausal patients of Kanchipuram District consisting of Poonamalle,Kundrathur and Sriperumbudur. Materials and Methods: A total of 5oo cases of peri and post menopausal women attending Gynec OPD for complains of abnormal uterine bleeding who underwent Pipelle endometrial biopsy and Hysterectomy were included for our study. Age: women of 35 years to 65 years were included for our study and the mean age of study was 50 years. Results: 34.4% of the patients had proliferative phase of the Endometrium.41.1% of the patients had Simple hyperplasia without atypia. Conclusion: Thus hormone treatment in the form of oral contraception and ovulation stimulation for family planning to hormone replacement therapy in menopause, to adjuvant therapy of tumors of the breast and uterus play a major role in Endometrial pathology.

Introduction

Hormone therapy is widely used throughout the world by women of all ages for a variety of reasons, ranging from oral contraception and ovulation stimulation for family planning to hormone replacement therapy in menopause, to adjuvant therapy of tumors of the breast and uterus. The histopathologic changes of the uterus, and particularly of the endometrium, associated with these therapies encompass a variety of morphologic features that are often difficult to interpret. The endometrium is a sensitive target tissue for steroid sex hormones and is able to modify its structural characteristics with promptness and versatility. The physiologic changes of the endometrium during reproductive life and after menopause reflect the influence of ovarian-secreted steroid sex hormones and of their withdrawal. Hormone manipulation in fertility problems and hormonal substitution therapy result in histologic patterns that do not fit the classical descriptions of the cyclic and involutional changes of the endometrium. Various combinations of hyperplastic, proliferative, secretory, and atrophic changes of endometrial glands, stroma, and blood vessels may result in confusing histologic patterns. As hormone therapy changes over time, with new regimens continuously being implemented, the effect on the endometrium can result in unpredictable structural changes.

The histologic patterns of the endometrium associated with hormone therapy vary with the dosage, duration of therapy, and individual hormone receptor activity. The same endometrium may display a number of changes under different conditions, resulting in a diversity of histologic patterns that may render some endometrial biopsies difficult to interpret. Although the endometrial response may vary from patient to patient, certain general histologic patterns for specific hormone therapies can be recognized. Endometrial hyperplasia and polyps can cause excessive bleeding during menstruation and/or vaginal bleeding between periods. They can also cause pelvic pain and sensitivity during and after intercourse and at other times during the month.Diagnosis:Usually we perform trans-vaginal ultrasound to evaluate the cause of bleeding. Unless the uterine lining is extremely thin, we take a sample of the endometrium and perform a biopsy. Hormonal changes of Endometrium. The endometrial tissue is a sensitive target for steroid sex hormones and is able to modify its structural characteristics with promptness and versatility. Here we discuss briefly endogenous hormonal effects (cyclic changes, luteal phase defect, unopposed estrogen effect) and describes the histologic patterns encountered in the most commonly used hormone therapies: oral contraceptives, ovulation stimulation, hormone replacement therapy, and antitumoral hormone therapy.

Oral contraceptives exert a predominant progestational effect on the endometriun, inducing an arrest of glandular proliferation, pseudosecretion, and stromal edema followed by decidualized stroma with granulocytes and thin sinusoidal blood vessels. Prolonged use results in progressive endometrial atrophy.

Ovulation induction therapy accelerates the maturation of the stroma and is often associated with a discrepancy between early secretory glands and an edematous or decidualized stroma with spiral arterioles.

Hormone replacement therapy with estrogen alone may result in continuous endometrial proliferation, hyperplasia, and neoplasia. The use of both estrogen and progesterone elicits a wide range of histologic patterns, seen in various combinations: proliferative and secretory changes, often mixed in the same tissue sample; glandular hyperplasia (in polyps or diffuse) ranging from simple to complex atypical; stromal hyperplasia and/or decidual transformation; epithelial metaplasia (eosinophilic, ciliated, mucinous); and inactive and atrophic endometrium.

Progesterone therapy for endometrial hyperplasia and neoplasia induces glandular secretory changes, decidual reaction, and spiral arterioles. Glandular proliferation is usually arrested, but neoplastic changes may persist and coexist with secretory changes.

Materials and Methods

In a period from 2012 August to 2014 July 500 Peri menopausal and post menopausal patients with the complaint of Abnormal Uterine Bleeding attending Gynec OPD were included in the study. Age of the patients vary from 35 years to 65 years were included for our study and the mean age of study was 50 years. For all the patients Routine investigations like Complete Haemogram, Liver Function Tests, Renal Function Tests, FBS,PPBS,Lipid profile, Serum Calcium levels were done. All these patients underwent Endometrial biopsy by Pipelle method and some Total Hysterectomy with Bilateral Salphingo Oopharectomy depending on the pathology.Biopsy was interpreted by an experienced Histopathologist.

Results:

Following table shows various pathological types and their distribution

Proliferative phase	Secretory phase	Irregular phase	Simple hyperplasia with out atypia
102	52	108	168

Irregular phase	Atrophic phase	Simple hyperplasia with atypia	Carcinoma endometrium
52	25	35	10

33.6% patients have simple hyperplasia with out atypia.[Fig – 4,5]21.6% of the patients have Irregular phase [Fig – 3] due to hormone therapy for abnormal uterine bleeding. Where as 0.2% have malignancy of Endometrium.[Fig – 6]

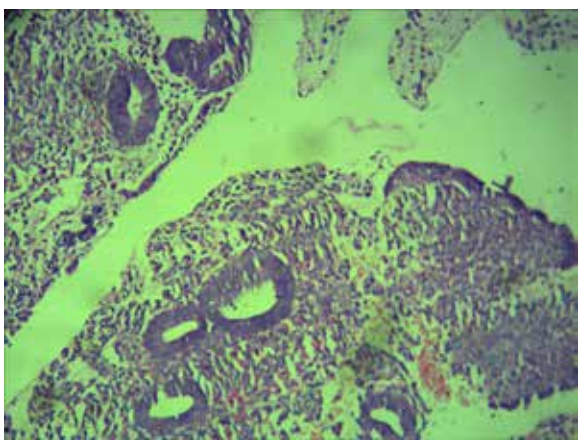

Fig – 1 Proliferative phase of the Endometrium

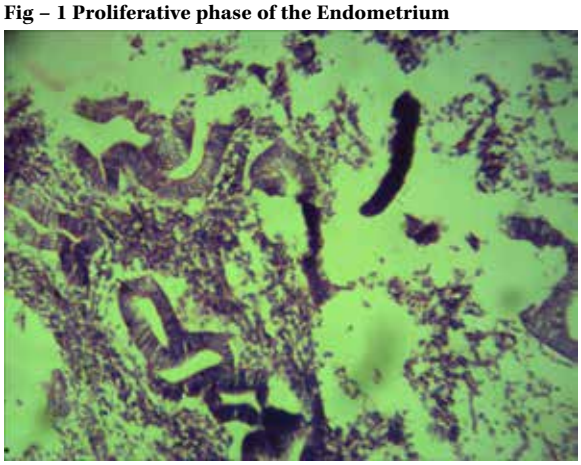

Fig – 2 Secretory phase of the Endometrium

Fig – 3 Irregular phase of the Endometrium

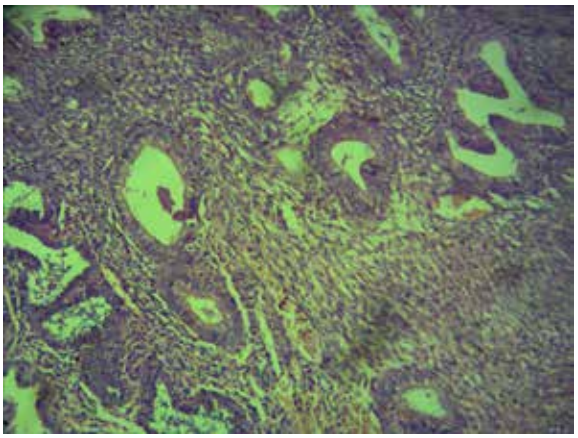

Fig – 4 Simple Hyperplasia with out atypia

Fig – 5 simple Hyperplasia with atypia

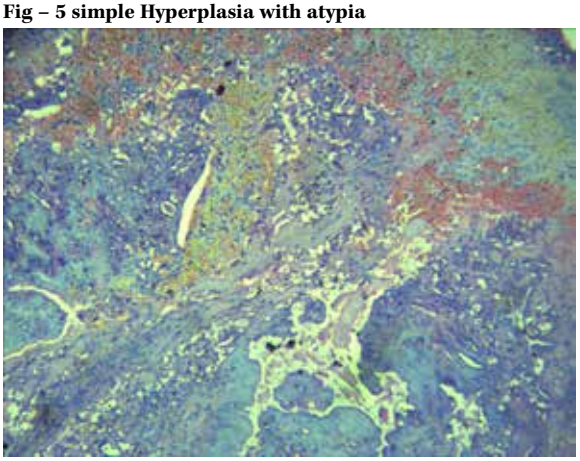

Fig – 6 Carcinoma Endometrium

Treatment

We treat hyperplasia medically or with minimally invasive surgery, depending on the reproductive goals and general medical condition of a patient. If endometrial hyperplasia is not found and a polyp is suspected, we perform diagnostic hysteroscopy in the office which can be extended to a hysteroscopic polypectomy (removal of the polyp) at the same time as needed. If more extensive therapy is indicated, hospital surgery may be necessary using minimally invasive techniques.

If you are suffering from chronic pelvic pain or abnormal vaginal bleeding, These symptoms should be diagnosed and treated as soon as possible – not merely to avoid greater problems, but, just as important, to ensure that your day-to-day life is as wonderful and carefree as it should be.

Conclusion:
Recognition of Simple Hyperplasia with or with out atypia is utmost important role of Pathologist to Hormonal imbalance and Malignancy.Infertility is a major complication of Hormonal imbalance so that has to be recognized as early as possible to prevent further consequences.

Discussion
During a woman's reproductive years, her endometrium undergoes cyclic changes. In response to estradiol synthesized by the growing follicle, intensive proliferation results in the build-up of an adequate endometrium. Following menstruation, the endometrium regenerates from the basal layer. Initially, its growth is horizontal until the entire uterine cavity is covered, and then it grows in thickness. This proliferative process slows down after ovulation and allows for secretory changes to take place as the emerging corpus luteum starts to secrete progesterone. Rather than further increasing in thickness, the endometrium undergoes qualitative changes and prepares for implantation in this phase. If implantation does not occur, the activity of the corpus luteum wanes and the hormonal support is withdrawn. The endometrium starts to break down and menstruation follows, signaling the onset of a new endometrial cycle.

In cases of oligo- or anovulation, the proliferative process may progress uninterrupted; if it lasts for a long time, it could become uncontrolled and give rise to hyperplastic changes and ultimately even to malignant transformation.[1]

Endometrial cancer is the fourth most common cancer in women.In the Western world, endometrial carcinoma is the most common malignant tumour of the female genital tract. Two different clinicopathological subtypes are recognised: the oestrogen-related (type I, endometrioid) and the non-oestrogen related (type II, non-endometrioid).It is associated with chronic anovulation, polycystic ovary syndrome (PCOS), the use of unopposed estrogen, and obesity (increased androgen to estrogen conversion by aromatase in adipose tissue).[2] Most endometrial cancers (90%) are of the endometrioid type and are associated with a relatively good prognosis, especially when the diagnosis is made early and the cancer is well-differentiated.

Endometrial cancer typically is diagnosed in menopausal women. The patient with long-standing ovulatory problems may be the exception, so women with PCOS are considered to be at higher risk. This study evaluated the risk for endometrial hyperplasia and cancer in women with PCOS.

PCOS is associated with several medical problems. Many patients seek care for signs of androgen excess, and others ask for regulation of their menstrual cycles. Women who are anovulatory may need help if they wish to conceive. However, PCOS also is associated with problems that affect general health. Impaired glucose tolerance, diabetes, hypertension, dyslipidemia, and metabolic syndrome are all more frequently diagnosed in women with PCOS.

Women who are obese and have a long history of anovulatory menstrual cycles are at risk for endometrial hyperplasia or cancer as well. Chronic anovulation exposes them to long periods of unopposed estrogen, which is a known risk factor for endometrial pathology. Women with PCOS have low levels of sex hormone-binding globulin, and therefore their bioactive steroid levels are higher. Insulin and insulin-like growth factor act at the level of the uterus and affect proliferation. Women who are obese have increased peripheral androgen-to-estrogen conversion by adipose tissue aromatase, adding to their estrogen exposure. It is, therefore, important to screen these women for endometrial pathology. The Pipelle biopsy is a simple yet accurate office procedure for this purpose. Hyperplasia and even early-stage, well-differentiated cancer can be managed medically, and for women who are infertile, the chance for future pregnancies can be maintained.[3,4]

This study did not find an increased risk for endometrial pathology in women with PCOS. Several possible reasons could explain this. Endometrial sampling was performed in only 13% of the women diagnosed with PCOS. Most patients had received medical treatment (contraceptive pill or metformin) before the endometrial sampling; therefore, they were at a low risk for abnormal findings. An important finding of this study is that women with positive histology had higher BMIs than the median BMI for the whole group. The BMI of the woman with endometrial cancer was 47.8 kg/m^2.

The finding of this study, that women with PCOS who received medical treatment (and therefore were exposed to progesterone on a regular basis) were at a comparable risk for endometrial pathology with the general population, is reassuring. However, we should not conclude, on the basis of these findings, that patients with PCOS who have long histories of unopposed estrogen exposure or those who have high BMIs do not need to be screened for endometrial pathology. We can certainly individualize the decision, but because the sampling procedure is relatively simple and is not associated with significant discomfort, we should test rather than miss cases of early endometrial pathology.

Endometrial Carcinoma
Endometrial carcinoma has become the most common invasive malignancy of the female genital tract in the United States. [8,9,10] The incidence is much lower in Asia, Africa, and South AmericaWell-documented conditions known to be associated with an increased risk of endometrial carcinoma include obesity, nulliparity, early menarche, and late menopause. Obesity appears to pose the greatest risk, especially patients 50 or more pounds over their ideal body weight. Aromatization of androstenedione to estrone, which occurs in peripheral fat, appears to be the source of the increased circulating levels of estrogen in obese patients. Diabetes mellitus hypertension, family history, a high-fat diet, and previous radiation have all been implicated in the increased incidence of endometrial carcinoma. Interestingly, a decreased rate of occurrence is seen in cigarette smokers; this has been explained by endometrial atrophy. However, smoking in conjunction with the use of exogenous estrogen significantly multiplies the risk of developing endometrial carcinoma, especially in thin women. The median age for diagnosis of endometrial carcinoma is about 60 years. Abnormal bleeding is the most common presenting symptom, but a few patients are asymptomatic. Because there is no adequate screening test for endometrial cancer, it is common practice to sample the endometrium of postmenopausal women who experience abnormal bleeding. The Pap smear, although adequate for screening for cervical intraepithelial neoplasia and carcinoma, has an unacceptably high false-negative rate for detecting endometrial cancer.

Endometrial carcinomas with associated hyperplasia tend to be well differentiated and have lesser degrees of myometrial invasion than lesions without such an association. Exogenous estrogen users have better-differentiated tumors than women who do not use estrogen. More aggressive variants of endometrial carcinoma, such as serous and clear cell carcinoma, are usually not associated with or preceded by hyperplasia. There are several experimental therapies for endometrial cancer under research. (Herceptin) has been used in cancers known to be positive for the Her2/neu oncogene, but research is still underway. Immunologic therapies are also under investigation, particularly in uterine papillary serous carcinoma. Early research has shown it to be effective in slowing the rate of cancer cell proliferation[5]. The CTNNB1 (beta-catenin) mutation is most commonly

mutated in the squamous subtype of endometrioid adenocarcinoma.[6] The International Federation of Gynecology and Obstetrics (FIGO), 2008 staging system for carcinoma of corpus uteri is as follows:[7]

- Stage IA* - No or less than half myometrial invasion
- Stage IB* - Invasion equal to or more than half of the myometrium
- Stage II* - Tumor invades cervical stroma but does not extend beyond the uterus**
- Stage III - Local and/or regional spread of the tumor
- Stage IIIA* - Tumor invades the serosa of the corpus uteri and/or adnexa †
- Stage IIIB* - Vaginal metastasis and/or parametrial involvement †
- Stage IIIC* - Metastases to pelvic and/or para-aortic lymph nodes
- Stage IIIC1* - Positive pelvic nodes
- Stage IIIC2* - Positive para-aortic lymph nodes with or without positive pelvic nodes
- Stage IV* - Tumor invasion of bladder and/or bowel mucosa and/or distant metastases
- Stage IVA* - Tumor invasion of bladder and/or bowel mucosa
- Stage IVB* - Distant metastases, including intra-abdominal and/or inguinal lymph node Cases of carcinoma of the corpus should be classified (or graded) according to the degree of histologic differentiation. The histopathology and degree of differentiation is as follows:
- Class G1 - Nonsquamous or nonmorular solid growth pattern of 5% or less
- Class G2 - Nonsquamous or nonmorular solid growth pattern of 6-50%
- Class G3 - Nonsquamous or nonmorular solid growth pattern of more than 50%

***Either G1, G2, or G3**

**Endocervical glandular involvement only should be considered as Stage I and no longer as Stage II

† Positive cytology has to be reported separately without changing the stage

REFERENCE

1. Chittenden BG, Fullerton G, Maheshwari A, Bhattacharya S. Polycystic ovary syndrome and the risk of gynaecological cancer: a systematic review. Reprod Biomed Online. 2009;19:398-405. | 2. Cramer DW. The epidemiology of endometrial and ovarian cancer. Hematol Oncol Clin North Am. 2012;26:1-12. | 3. Randall TC, Kurman RJ. Progestin treatment of atypical hyperplasia and well-differentiated carcinoma of the endometrium in women under age 40. Obstet Gynecol. 1997;90:434-440. | 4. Kovacs P, Matyas S, Ungar L. Preservation of fertility in reproductive-age women with the diagnosis of cancer. Eur J Gynaecol Oncol. 2008;29:425-434. | 5. Suh, DH; Kim, JW; Kang, S; Kim, HJ; Lee, KH (2014)." Major clinical Research advances in gynecologic cancer in 2013 "Journal of Gynecologic Oncology, 25(3): 236–248. | 6. Colombo, N; Preti, E; Landoni, F; Carinelli, S; Colombo, A; Marini, C; Sessa, C (2011). "Endometrial cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up".Annals of Oncology 22 (Supplement 6): vi35–vi39. | 7. Creasman WT. Revised FIGO staging for carcinoma of the vulva, cervix and endometrium. Inter J Gynecol and Obstet. 2009;105:103-4. | | | | 8.Hendrickson MR, Ross JC, Kempso RL: Toward the development of morphologic criteria for well differentiated adenocarcinoma of the endometrium. Am J Surg Pathol 7: 819– 838, 1983 | | 9.Glassburn JR: Carcinoma of the endometrium. Cancer 48: 575– 581, 1981 | 10.Creasman WT, Morrow CP, Bundy BN et al: Surgical pathologic spread patterns of endometrial cancer: A Gynecologic Oncology Group study. Cancer 60: 2035– 2041, 1987 |