Premalignant Conditions of the Endometrium

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Abstract

In developed countries, endometrial carcinoma is the most common female genital tract malignancy. It is showing an increasing trend in India as well. It is now recognized that a precursor lesion usually precedes it. The distinction between endometrial hyperplasia and true precancerous lesions is of utmost importance to provide appropriate intervention. At present, the endometrial intraepithelial neoplasia (EIN) classification best fits this requirement as compared to the more widely used four-class World Health Organization schema (1994), which does not distinguish between atypical hyperplasia and precancerous lesions.

The diagnosis of premalignant lesions is made by dilatation and curettage or endometrial suction curette, but the accuracy of both in diagnosing precancer and excluding concurrent carcinoma is unclear. Hysteroscopy with directed biopsy improves the sensitivity of diagnosis. Total hysterectomy for endometrial intraepithelial neoplasia allows definitive assessment of a possible concurrent carcinoma and effectively treats premalignant lesions. However, for women who wish to retain their childbearing potential, systemic or local progestin therapy has a role as an alternative to hysterectomy.

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R. Patni (ed.), *Current Concepts in Endometrial Cancer*,
DOI 10.1007/978-981-10-3108-3_3

Introduction

Globally, endometrial cancer is the fifth most common cancer in women, affecting 318,000 women every year [1]. While it is the most common female genital tract malignancy in the West, accounting for almost half of all new gynecologic cancers [2], in India, the incidence is low with an age-standardized incidence rate of 4.6 per 100,000 population [3].

Two main types of endometrial cancer are recognized: type 1 cancers that constitute 80–90 % of cases are estrogen-dependent endometrioid adenocarcinomas with good prognosis. On the other hand, type 2 tumors which are non-estrogen dependent are found to be more aggressive with poor prognosis carrying a high risk of relapse and metastasis.

The most common type of endometrial carcinoma is the endometrioid subtype (approximately 80–85 % of cases), which is preceded by a precursor lesion. Excess estrogenic stimulation of the endometrium, with consequent proliferative glandular epithelial changes, has been associated with both endometrioid endometrial carcinoma and its precursor lesions. Risk factors known to predispose to the development of endometrial carcinoma are obesity, unopposed estrogen therapy, diabetes mellitus, and nulliparity. Women most commonly present with abnormal uterine bleeding, whether in the form of menorrhagia, metrorrhagia, or postmenopausal bleeding, while some may present with abnormal Pap smear, i.e., atypical glandular cells or atypical endometrial cells, detected on routine Pap smear.

Endometrial Hyperplasia Classification Systems

Currently there are two systems of endometrial precancer classification: (1) the WHO 1994 schema and (2) the endometrial intraepithelial neoplasia (EIN) diagnostic schema developed by the International Endometrial Collaborative Group [2]. The WHO 1994 schema classifies histology based on glandular complexity and nuclear atypia into four categories of risk classification: (1) simple hyperplasia, (2) complex hyperplasia, (3) simple hyperplasia with atypia, and (4) complex hyperplasia with atypia. These categories, being descriptive in nature, make interpretation more subjective. Importantly, this classification does not provide specific management algorithms. Due to poor reproducibility of the WHO classification [3, 4], the EIN schema was introduced to improve clinical management.

There are three categories in EIN schema based on pathologic criteria [5, 6]: (1) benign (benign endometrial hyperplasia), (2) premalignant (endometrial intraepithelial neoplasia), and (3) malignant (endometrial adenocarcinoma, endometrioid type, well differentiated). Tables 3.1 and 3.2 show the diagnostic criteria and definitions of EIN, respectively. Using this classification, pathologists can classify the lesion more accurately, and clinicians can guide treatment appropriately. It has been shown to be a good prognostic tool in several retrospective studies and one prospective study [7–9], with better interobserver reproducibility than the WHO 1994 schema. Figures 3.1 and 3.2 are images of benign endometrial hyperplasia and endometrial intraepithelial neoplasia, respectively.

Table 3.1 Diagnostic criteria for endometrial intraepithelial neoplasia [6, 7]

Nomenclature	Topography	Functional category	Treatment
Benign endometrial hyperplasia	Diffuse	Prolonged estrogen effect	Hormonal therapy, symptomatic
Endometrial intraepithelial neoplasia	Focal progressing to diffuse	Precancerous	Hormonal therapy or surgery
Endometrial adenocarcinoma, endometrioid type, well differentiated	Focal progressing to diffuse	Malignant	Surgery, stage based

Table 3.2 Definitions of endometrial intraepithelial neoplasia criteria [6, 7]

Criteria	Comments
Architecture	Area of glands greater than stroma (volume percentage stroma less than 55 %)
Cytology	Cytology differs between architecturally crowded focus and background
Size greater than 1 mm	Maximum linear dimension exceeds 1 mm
Exclude mimics	Benign conditions with overlapping criteria (i.e., basalis, secretory, polyps, repair)
Exclude cancer	Carcinoma if maze-like glands, solid areas, or appreciable cribriform

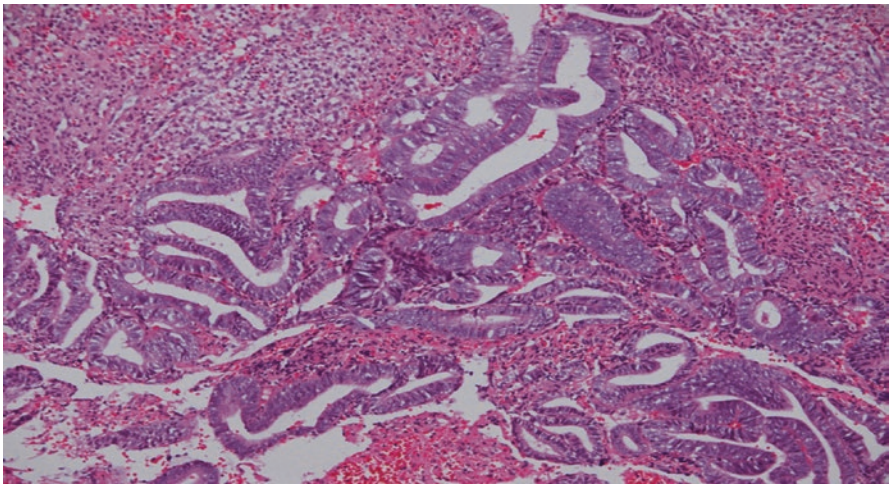

Fig. 3.1 Benign endometrial hyperplasia (Picture courtesy of Dr. Sandeep Mathur)

Precancer Diagnosis: Endometrial Sampling and Imaging

The management of patients with premalignant endometrial lesions requires accurate diagnosis of a precancer lesion and exclusion of coexisting carcinoma to prevent any under- or overtreatment. Ideally, it should be possible to make this diagnosis

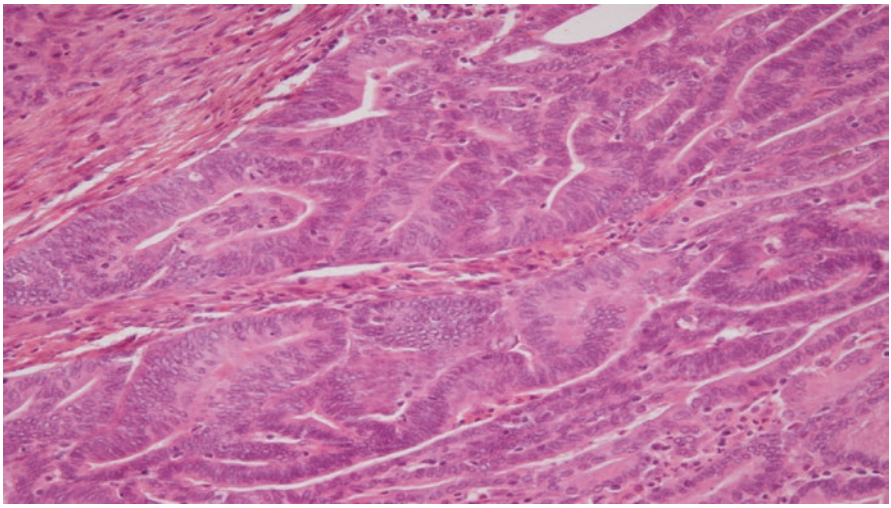

Fig. 3.2 Endometrial intraepithelial neoplasia (Picture courtesy of Dr. Sandeep Mathur)

preoperatively. However, it has been seen that in approximately 40 % of patients who had a diagnosis of endometrial intraepithelial neoplasia diagnosis by endometrial suction curette, the diagnosis changed to carcinoma after hysterectomy [8, 10], making exclusion of concurrent carcinoma a challenge.

Both dilatation and curettage (D&C) and endometrial suction curette have pitfalls in diagnosing precancer and excluding concurrent carcinoma. Both have sampling limitations: approximately 60 % of D&C specimens sample less than one half of the uterine cavity [11]. For women undergoing hysterectomy as a definitive management for premalignant lesions, the technique of sampling does not matter as much since hysterectomy eliminates the risk of failure to diagnose an endometrial cancer. Dilation and curettage and endometrial suction curette sampling devices have been reported to yield equal rates of cancer detection in patients with abnormal uterine bleeding [12]. The more accurate diagnosis of uterine lesions is made by hysteroscopy with directed biopsy as it helps in visual assessment of the background epithelium also [13–15]. It gives the best opportunity to confirm the diagnosis of a true premalignant endometrial lesion and exclude an associated endometrial carcinoma. Currently available diagnostic methods provide very little amount of endometrial tissue making cancer risk assessment less feasible. So it has been suggested that the assessment of sample adequacy should be included in the diagnostic scheme as is done for cervical cytology specimens.

In women with postmenopausal bleeding, transvaginal ultrasonography (TVS) is the most common employed imaging modality due to high specificity in excluding carcinoma. Endometrial sampling is not recommended if endometrial thickness is found to be 4 mm or less because of the very low risk of uterine malignancy in these patients [16]. An endometrial thickness greater than 4 mm in a patient with postmenopausal bleeding requires additional evaluation (such as sonohysterography,

office hysteroscopy, or endometrial biopsy) to adequately visualize endometrial thickness. The significance of an endometrial thickness greater than 4 mm in an asymptomatic, postmenopausal patient has not been established, and this finding need not routinely trigger evaluation [16].

Unlike postmenopausal women, the role of TVS is limited in premenopausal women as endometrial thickness is not static during different phases of the menstrual cycle and may overlap with women having carcinoma.

The role of tumor markers for endometrial carcinoma is not well established. An inexpensive, sensitive, and specific serum test, which would be the most attractive approach to screen women for endometrial cancer, has still not been discovered. Raised serum CA 125 usually signifies an advanced disease and a poor prognosis but has limited role in monitoring treatment response. The serum markers CA 19-9, CA 15-3, and CA 72-4 and CEA levels are raised in endometrial cancer patients in 22–24 %, 24–32 %, 22–32 %, and 14–22 % of cases, respectively [17]. It has been seen that only a combination of CA 125 and CA 19-9 has a role in posttreatment surveillance due to high sensitivity (83.3 %) for detection of recurrence, with only 12.8 % of false-positive cases [17]. Tumor markers should be used in conjunction with other modalities, such as ultrasound and high-resolution MRI to attain high specificity.

Management of Endometrial Intraepithelial Neoplasia

Management of a newly diagnosed case of endometrial intraepithelial neoplasia has the following main objectives: (1) to exclude a concurrent adenocarcinoma, (2) to minimize the risk of delayed discovery of an occult carcinoma, and (3) to prevent progression to endometrial cancer.

Nonsurgical Management Options

Nonsurgical management is advised to patients (1) whose clinical, radiological, and pathological assessment suggests endometrial hyperplasia without any evidence of malignancy and (2) who desire future fertility (3) or patients with sufficient medical comorbidities precluding surgical management.

Presently nonsurgical management options include hormonal therapy and endometrial ablation. Endometrial ablation using thermal or electrical cautery devices has been employed for non-precancerous endometrial lesions, but it is not recommended for the treatment of atypical endometrial hyperplasia (AEH)/endometrial intraepithelial neoplasia (EIN). The completeness of ablation cannot be guaranteed via any method, and subsequent adhesions may make the cavity less accessible for follow-up surveillance.

Several studies have evaluated the use of hormonal treatment to induce regression of hyperplasia. Progestins are widely used with acceptable toxicity profile. Progesterone counteracts the mitogenic effects of estrogens and induces

secretory differentiation [22]. Treatment with progestins may be an option for any patient who wants to retain childbearing, any patient with a hyperplastic or precancerous lesion who desires uterine preservation, and most elderly patients with medical comorbidities having diagnosis of endometrial intraepithelial neoplasia, a low-grade malignancy, or both. Although the efficacy of progesterone is well recognized, the exact dose and duration has not been specified till date [23–25]. Neither has the frequency been determined whether treatment should be cyclic or continuous. The appropriate length of follow-up after treatment also is still debatable.

Table 3.3 shows commonly used progestin regimes. Medroxyprogesterone acetate and megestrol acetate, with different doses and schedules, are the most common progestin therapies used in the clinical setting. Regression of hyperplasia (simple, complex, and atypical) has been observed in 80–90 % of individuals receiving medroxyprogesterone acetate (10 mg daily for 12–14 days per month) or micronized progesterone in vaginal cream (100 mg for 12–14 days per month) when treated for 3 months as shown in Table 3.3 [26–28]. Long-term systemic medical treatment to prevent reappearance of endometrial intraepithelial neoplasia requires awareness of concomitant adverse effects. Edema, gastrointestinal disturbances, and thromboembolic events are infrequent with these treatments, thereby making medical management a suitable therapeutic option for patients for whom surgical management is not desired. However, if endometrial intraepithelial neoplasia is present, there is a higher incidence of failure of medical management and subsequent development of cancer [29].

The levonorgestrel-releasing intrauterine system (levonorgestrel IUS) is another preferred option in these cases. The greatest advantage is a onetime insertion and the IUS is effective for a period of 5–7 years. Local-acting progesterone has an effect on the endometrium that is several times stronger than that exerted by systemic products and has a decreased systemic effect. A systematic review and meta-analysis found a pooled regression rate of 69 % (95 % confidence interval, 58–83) in 14 studies ($n = 189$) of women with atypical hyperplasia treated with oral progestins [30].

Follow-up and surveillance is important and is done by serial endometrial sampling every 3–6 months, but the appropriate frequency has not yet been determined.

Table 3.3 Hormonal treatment for endometrial intraepithelial neoplasia

Hormonal agent	Dosage and length
Medroxyprogesterone acetate	10–20 mg/day, or cyclic 12–14 days per month
Depot medroxyprogesterone	150 mg intramuscularly, every 3 months
Micronized vaginal progesterone	100–200 mg/day or cyclic 12–14 days per month
Megestrol acetate	40–200 mg/day
Levonorgestrel intrauterine system	52 mg in a steroid reservoir over 5 years

Modified from Trimble et al. [31]

Surgical Assessment and Management Options

In a woman who does not desire future fertility, total hysterectomy is the most preferred treatment option as it fulfills all the three objectives stated above. It gives a definitive diagnosis of possible concurrent carcinoma and effectively treats premalignant lesions. Hysterectomy can be performed via abdominal, vaginal, or minimally invasive procedures with or without bilateral salpingo-oophorectomy. Supracervical hysterectomy, morcellation, and endometrial ablation should not be performed for treatment of endometrial intraepithelial neoplasia because of concerns about underlying carcinoma [17]. Removal of the cervix and lower uterine segment along with the uterine corpus permits staging of any incidentally discovered cancer and reduces the risk of leaving behind residual disease. The possible need for additional surgery to complete surgical staging in case a carcinoma is identified should be explained to the patient clearly.

Intraoperatively, management may be altered based on intraoperative assessment and pathologic review. The specimen should be examined for gross evidence of a tumor or myoinvasion, which may require frozen section. This can help guide decisions about the need for comprehensive surgical staging, but the diagnostic accuracy of frozen section should be kept in mind as it varies from institution to institution. The correlation between frozen section and final pathology for histology, grade, and depth of myometrial invasion has been reported to be as high as 97.5 %, 88 %, and 98.2 %, respectively [18]. Furthermore, high-risk disease is detected more efficiently in frozen section compared with low-risk disease [19].

Comprehensive surgical staging with pelvic and para-aortic lymph node dissection at the time of hysterectomy for endometrial intraepithelial neoplasia is not recommended as it may result in overtreatment and increased surgical risk for a vast majority of patients. The risk of a concurrent high-risk uterine carcinoma with features like high-grade tumor, deep invasion, or lymphovascular space invasion, in women with a biopsy diagnosis of endometrial intraepithelial neoplasia, is approximately 10 % [10, 20].

Vaginal hysterectomy may be performed if the need for comprehensive surgical staging is excluded completely, as this is not feasible with a vaginal approach. Bilateral salpingo-oophorectomy is not absolutely required, especially in premenopausal women, and, in fact, removal of both ovaries in premenopausal or perimenopausal women without a confirmed gynecologic malignancy may increase overall morbidity and mortality [21].

As far as prevention is concerned, a healthy lifestyle, including adequate physical activity, daily exercise, healthy diet, and control of weight and blood sugar levels, is essential. Because endometrial intraepithelial neoplasia is often an antecedent of endometrial cancer, clinicians may counsel patients about weight loss or bariatric surgery to reduce the risk of progression/recurrence as obesity is one of the major risk factors for endometrial cancer.

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